



# Neglected tropical diseases and One Health

Gearing up against antimicrobial resistance  
to secure the safety of future generations

Meeting report, 24 November 2020



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## 1. Introduction

A WHO webinar on neglected tropical diseases (NTDs) and antimicrobial resistance was held virtually on 24 November 2020 as part of World Antimicrobial Awareness Week. The agenda is annexed to this report.

World Antimicrobial Awareness Week aims to increase awareness of global antimicrobial resistance and encourage best practices among the general public, health workers and policy-makers to avoid the further emergence and spread of drug-resistant infections. A global action plan to tackle the growing problem of resistance to antibiotics and other antimicrobial medicines was endorsed by the Sixty-eighth World Health Assembly in May 2015. One of its key objectives is to improve awareness and understanding of antimicrobial resistance through effective communication, education and training. World Antimicrobial Awareness Week is observed annually from 18 to 24 November.

Participants were welcomed to the meeting by representatives of the WHO Department of Control of Neglected Tropical Diseases and reminded of the meeting's full title, "Neglected tropical diseases and One Health: gearing up against antimicrobial resistance to secure the safety of future generations". It was further noted that the discussion was taking place as the world observes Antimicrobial Awareness Week (18–24 November 2020).

Most NTD programmes depend on several medicines to scale up interventions for the control, elimination and eradication of these diseases. As such, it is critical and was agreed to take part actively in the movement to preserve antimicrobial medicines. The theme of this year's campaign – *United to preserve antimicrobials* – is well aligned with the identification of antimicrobial resistance in the NTD road map for 2021–2030 as one of the risks that requires close monitoring in both humans and animals to reduce the potential negative impact on limited NTD therapeutic arsenals.

Antimicrobials are part of the arsenal that the NTD community has at its disposal to save lives and are critical in many ways to treat both common and more serious infections. Whenever antimicrobials are used, however, they have the potential to cause side-effects and contribute to various types of resistance; this constitutes today a potential threat to public health.

Participants heard that the wider Antimicrobial Awareness Week would include wide-ranging discussions to raise awareness about antimicrobial resistance, how and when antimicrobials should be taken, how populations can remain healthy, and how the fight against resistance can ensure these treatments remain available for future generations.

For NTDs specifically, the potential emergence of drug resistance is real: many programmes depend heavily on antimicrobials for preventive and curative chemotherapy. Widespread resistance to currently used medicines has the potential, therefore, to jeopardize entire interventions and put at risk global programmes that currently treat millions of marginalized populations.

The aim of the webinar was to increase awareness of global antimicrobial resistance, to explore related issues and to encourage best practices among stakeholders and policy-makers to avoid the emergence and spread of drug-resistant infections in general and for NTDs in particular.

The webinar featured simultaneous interpretation in English, French and Spanish. Participants were invited to ask questions during the proceedings via the Slido application. The meeting was held online via Zoom and was also streamed live on YouTube.

The webinar was moderated by Professor Santiago Mas-Coma, with contributions from Professor Emmanuelle Cambau, Professor Bruno Levecke, Professor Shyam Sundar, Dr Oriol Mitjà, Dr Catherine Oldenburg, Dr Daniel Argaw Dagne and Professor Mas-Coma himself.

## 2. Antimicrobial resistance in the context of NTDs

The first presentation was made by Dr Haileyesus Getahun, Director, WHO Global Coordination and Partnership department for Antimicrobial Resistance, and addressed antimicrobial resistance in the context of NTDs starting with a wide-ranging overview of the field.

Antimicrobial resistance is a complex issue involving humans, animals, plants, food chains and the environment as a whole. The critical issue, Dr Getahun noted, is that antimicrobials are shared between all these spheres. The challenge, therefore, ranges from underuse and misuse to overuse of antimicrobials, with the potential to negatively affect human, animal and plant safety, food security and global health security. That is why WHO has taken steps in the past 2 years and established a new division led by an Assistant Director-General to boost its leadership in coordinating the global response and the tripartite (WHO/FAO/OIE) joint action on antimicrobial resistance.

That response includes supporting and coordinating the delivery of World Antibiotic Awareness Week. This year, Dr Getahun noted, the Week has been expanded to include antivirals, antifungals and anti-parasitics in addition to antibiotics. It will be called World Antimicrobial Awareness Week from 2020 onwards and its dates are now fixed from 18 to 24 November every year. The fundamental issue is that drug resistance is not limited to antibiotics: a collective response is paramount to address problems that have the potential to intersect multiple fields. Dr Getahun noted that the strong commitment of the NTD community, as evidenced by the representation at the webinar, signalled that difficult issues were not being avoided and that they might best be addressed collectively.

Synergy and efficient interaction between the different publics and programmes would be vital to ensure that antimicrobials are properly addressed by the NTD community in general and by individual programmes more specifically, in order to safeguard past gains and ensure that effective treatments continue to be administered in the future..



### 3. Antimicrobial use and resistance to commonly used NTD medicines

There followed a presentation on antimicrobial use-cases and antimicrobial resistance threats or concerns encountered and likely to be faced in the context of commonly used NTD medicines.

Dr Daniel Argaw Dagne, WHO Department of Control of Neglected Tropical Diseases, began by stating that NTDs include more than 20 diseases and disease groups that are caused by helminthic parasites, viruses, bacteria, protozoa, fungi and ectoparasites, as well as the noncommunicable disease snakebite envenoming.

NTDs are responsible for tremendous morbidity and mortality, leaving in their wake major disability, disfigurement, stigmatization and discrimination.

One major strategic intervention used to combat NTDs is preventive chemotherapy. This approach has enabled more than 1 billion people to be treated annually every year since 2016. In the context of NTDs requiring individual or intensive case management, more than 1 million life-saving treatments were delivered in 2019 alone. These figures show the scale at which the NTD community uses antimicrobials for the prevention, elimination and overall control of these diseases.

### 4. NTDs and One Health

Mass treatment and case management are complemented by integrated vector management, water, sanitation and hygiene (WASH) programmes and by veterinary public health strategies. Together, all these categories of intervention may work most synergistically by adopting a more comprehensive One Health approach.

One Health is defined as:

an approach to designing and implementing programmes, policies, legislation and research in which multiple sectors communicate and work together to achieve better public health outcomes. The areas of work in which a One Health approach is particularly relevant include food safety, the control of zoonoses (diseases that can spread between animals and humans, such as flu, rabies and Rift Valley Fever), and combatting antibiotic resistance (when bacteria change after being exposed to antibiotics and become more difficult to treat).<sup>1</sup>

A significant number of NTDs are also of zoonotic origin; the One Health approach is particularly relevant in these cases. The One Health strategy is also particularly relevant to the prevention of antimicrobial resistance development – a focus, Dr Argaw Dagne noted, of further contributions to the webinar.

Dr Argaw Dagne then presented an overview of the commonly used medicines for treatment of NTDs – provided to the participants less as an exhaustive picture of the resistance status or surveillance status of antimicrobials in all NTD medicines, but rather to demonstrate the number and types of medicines that are commonly used to treat NTDs, as well as the status of antimicrobial resistance and the concerns associated with each disease (*Fig. 1*).

\* What is “One Health”? In: One Health [website]. Geneva: World Health Organization; 2021 <https://www.who.int/news-room/q-a-detail/one-health>, accessed 2 March 2021).

**Fig. 1. Status of antimicrobial resistance to commonly used NTD medicines, by disease**

Disease	Medicines commonly used for treatment	Antimicrobial resistance threat
Buruli ulcer	Rifampicin, clarithromycin, streptomycin	Resistance has been reported to rifampicin and streptomycin to <i>Mycobacterium ulcerans</i> isolates; development of cross-resistance is a concern as rifampicin is used to treat tuberculosis, leprosy and other diseases
Chagas diseases	Nifurtimox, benznidazole	Geographical variation in therapeutic response due to various factors including the discrete typing unit of <i>Trypanosoma cruzi</i> , inoculum and infection, but no evidence for antimicrobial resistance
Dengue and chikungunya	NA	NA
Dracunculiasis	NA	NA
Echinococcosis	Benzimidazoles – albendazole and mebendazoles, and praziquantel	Medical treatment is only one of the options for clinical management; low evidence for resistance and no gold standard methods available to determinate biological status and response to treatment
Foodborne trematodiasis	Triclabendazole	Resistance has been reported in areas where resistance to veterinary infections occur
Human African trypanosomiasis	Suramin, pentamidine, melarsoprol, nifurtimox, eflornithine, fexinidazole	Melarsoprol resistance to <i>Trypanosoma brucei gambiense</i> has been reported in the past; no drug resistance in the recent past for other medicines
Leishmaniasis	Amphotericin B deoxycholate or liposomal, sodium stibogluconate, meglumine antimoniate, paromomycin, miltefosine	Sodium stibogluconate resistance to Leishmania in South-East Asia; reduced treatment response rate of miltefosine in Nepal, South-East Asia; use of miltefosine in Latin America and Europe for canine treatment is a threat; single-dose AmBisome (liposomal amphotericin B) is a concern for development of resistance
Leprosy	Rifampicin, dapsone, clofazimine, ofloxacin, minocycline	Resistance has been reported to most of the antileprosy medicines although from small samples
Lymphatic filariasis	Albendazole, diethylcarbamazine, ivermectin	Suboptimal responses develop after many years of MDA; combination therapies such as IDA reduce development of resistance
Mycetoma	Trimethoprim-sulfamethoxazole, amikacin, itraconazole, ketoconazole	Treatment response is higher in actinomycetoma; generally, clinical response to antifungals is poor despite long duration
Chromoblastomycosis and other deep mycoses	Itraconazole, terbinafine, other azoles	Long duration of treatment with increased risk for resistance; treatment refractory is common; no resistance monitoring
Onchocerciasis	Ivermectin	Suboptimal responses and treatment failures have been reported
Schistosomiasis	Praziquantel	No resistance reported
Soil-transmitted helminthiasis	Albendazole, mebendazole	Reported low efficacy for hook worm infection
Rabies	Antirabies vaccines	NA
Scabies and other ectoparasitoses	Ivermectin, permethrin cream or benzyl benzoate lotion	No substantial evidence for resistance of <i>Sarcoptes scabiei</i> for permethrin cream or ivermectin; treatment inefficacy is usually associated with management (application errors, compliance), re-infestation, etc.
Snakebite envenoming	Antivenoms	NA
Trachoma	Azithromycin, tetracycline eye ointment	No evidence for resistance to azithromycin following mass treatment for trachoma
Taeniasis and cysticercosis	Niclosamide, praziquantel	No documented resistance; no systematic resistance surveillance
Yaws	Azithromycin, benzathine penicillin	Emergence of resistance to azithromycin in yaws ( <i>Treponema pallidum pertenuis</i> ) treatment has been reported recently

IDA: ivermectin-diethylcarbamazine-albendazole; MDA: mass drug administration; NA: not applicable

Dr Argaw Dagne concluded his presentation by summarizing the key issues.

- Antimicrobial resistance could lead to potential disruption of many NTD programmes.
- Many NTDs have few therapeutic alternatives to antibiotics, and many of these treatments have been in use for decades.
- There is no systematic monitoring for or surveillance of antimicrobial resistance for most NTDs.

He then noted a need to establish close monitoring of treatment efficacy as well as resistance surveillance and monitoring mechanisms, which would include the development of guidance documents.

Improving use of animal vaccines would reduce the need for antiparasitic treatments also, he noted, thereby reducing drug pressures. Similarly, it might also be necessary to promote the use of different medicines to treat zoonotic and human infections.

Dr Argaw Dagne noted that validated biomarkers are lacking for effective monitoring of antimicrobial resistance in the case of most NTDs and that the NTD community should advocate to benefit from current movements and attention to the prevention of and monitoring for resistance and related initiatives.

## 5. Antimicrobial resistance in NTD treatment

After thanking Dr Dagne for his presentation, webinar moderator Professor Mas-Coma introduced Professor Emmanuelle Cambau, a medical doctor and academic at the University of Paris, who addressed the issue of antimicrobial resistance in her specialist field of leprosy.

### 5.1 Leprosy

Beginning with an historical overview, Professor Cambau noted that antimicrobial resistance in treatment of leprosy started as soon as a good antibiotic was found (dapson, given as monotherapy from 1950 to 1982). Resistance was observed some years after, when treatment expanded to include rifampicin too. Subsequently, when the leprosy community began using ofloxacin, not initially developed as an antileprosy medicine, resistance was observed. Multidrug combination therapy with dapson, rifampicin and clofazimine was developed with the idea of avoiding resistance in mind.

Difficulties in assessing resistance arise, Professor Cambau stated, because the causative *Mycobacterium leprae* bacterium does not grow in vitro. Therefore, the only phenotypic test consists of inoculating mice in their hind footpad and treating them with antibiotics for 1 year, because the *M. leprae* doubling time is far longer than that of other bacteria (some 10 days or more), whereas for *E. coli*, for example, it is just 20 minutes.

Professor Cambau referenced the genotypic assessment of *M. leprae* resistance published by WHO in 2009 and updated in 2017<sup>1</sup> before proposing three methods for detecting resistance in all affected countries. The first method would be polymerase chain reaction for mutations associated with antimicrobial resistance, the second would be a commercially available gene line-probe assay, while the third would involve genome sequencing, which is more difficult, since it requires an expert laboratory.

In light of this, a first prospective survey on antimicrobial resistance was published, thanks to the WHO surveillance network. This showed that of 2000 cases studied from among 200 000 cases per year, a rate of 8% resistance to dapson, rifampicin or ofloxacin was observed.

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\* A guide for surveillance of antimicrobial resistance in leprosy: 2017 update. Geneva: World Health Organization; 2017 (<https://apps.who.int/iris/rest/bitstreams/1137285/retrieve>, accessed 19 March 2021).

The two countries with the most cases of leprosy are India and Brazil, where more than 10 drug-resistant cases have been detected; Indonesia has 3-10 cases per year. Even African countries, which have low level resistance, have shown resistance in relapse cases, but also in new cases.

Professor Cambau then stated the desired objectives of surveillance for antimicrobial resistance in leprosy. These include ensuring the ability to determine *M. leprae* resistance to rifampicin on its own and when combined with dapson and/or ofloxacin. It would be desirable, she stated, to concentrate on new leprosy cases and on retreatment cases, and to monitor resistance rates over time, as well as to provide information on patient/geographical location characteristics, i.e. in who and in which locations cases with resistant strains are observed.

Professor Cambau presented four conclusions to the meeting.

- Antimicrobial resistance exists in the treatment of leprosy by rifampicin, dapson and ofloxacin.
- Surveillance for antimicrobial resistance in leprosy is organized by WHO, supported by nongovernmental organizations and is part of the strategy to reach zero leprosy.
- Current multidrug combination therapy may not be efficient for ever; thus research on new leprosy medicines is needed.
- Resistance may result from previous treatment but may stem also from the general use of antimicrobials.

Professor Cambau ended her presentation by stating her belief that a medical commitment is needed outside of the leprosy field not to overuse antimicrobial agents, commenting that this made the present webinar conference so vitally important.

## Discussion

In the ensuing discussion, Professor Mas-Coma began by asking about the possibility of cross-resistance between the different medicines used to treat leprosy, to which Professor Cambau responded that, to date, this did not seem to occur. What has been observed is co-resistance or an association of resistances. For instance, a patient was treated with dapson monotherapy then with rifampicin monotherapy. The strain became resistant to dapson and to rifampicin, resulting in a multidrug resistant strain. This was observed in new patients and relapse patients several times. Fortunately, however, there is no cross resistance between the medicines, unless of course it occurs unbeknownst to scientists; this, however, is difficult to determine.

In a subsequent question about the best practice advice to countries in order to prevent antimicrobial resistance in leprosy treatment, Professor Cambau replied that leprosy treatment is given as a multidrug therapy and that this is not a problem in itself. There are two problems that arise, however: the first lies in giving these medicines outside of the leprosy field. Ofloxacin and rifampicin are given for other purposes; therefore, Professor Cambau advised that there be supervised treatment and controls in the selling of these medicines so as to ensure that overuse does not occur. This would constitute best advice. There is also a concern about preventive treatment, which is now being advocated for leprosy.

To a further question about assuring quality in in-country laboratories that perform testing for antimicrobial resistance in leprosy, Professor Cambau assured the meeting that this is not too difficult. If the laboratory is used to detecting resistance in *M. tuberculosis*, for instance, there will be a specialized laboratory in each country. If there is capacity for *M. tuberculosis* resistance testing, there is capacity for leprosy. External quality control can also be done quite easily; the only requirement is that the laboratory doing this be close enough to patients and not too far from reference centres either.

## 5.2 Yaws

Dr Oriol Mitjà, Associate Professor of Infectious Diseases at the University of Barcelona, addressed the meeting with a presentation on antimicrobial resistance in the treatment of yaws. He began by discussing resistance to azithromycin in yaws and resistance mechanisms in *Treponema pallidum pertenuis*. These bacteria can lead to deformity and ulcers in the skin of affected children, but in 2012 it was shown that a single dose of azithromycin given orally can cure the disease. Currently, azithromycin is being used to implement an ambitious WHO strategy to eradicate the disease, and mass drug administration (MDA) is being implemented in some countries in Africa and the Pacific Islands.

The resistance mechanisms in *Treponema spp.* are two major mutations targeting the two genomic copies of the TP23S gene: A2058G and A2059G. Mutations in RNA spoil the effect of azithromycin. Detection of macrolide resistance was observed in Papua New Guinea – the detection process itself is similar to that in syphilis. Subsequently, two mechanisms or two techniques have been used to detect the mutation. One involves direct sequencing to identify the two main mutations: A2058G and A2059G. The second technique is the most commonly used, a restriction fragment length polymorphism analysis in which restriction enzymes are used to recognize DNA sequence variations so that the DNA sample is digested into fragments and the resulting restriction fragments are then separated by gel electrophoresis according to their size.

Dr Mitjà's professional experience of antimicrobial resistance, he stated, was centred around an MDA programme in which 20 000 people were treated. MDA gave an observed prevalence of 1.8 active yaws cases in that population, equating to approximately 400 yaws cases. There was no indication of resistance or treatment failures initially, but in remaining cases that had to be treated in subsequent years, resistance became apparent. At month 36, Dr Mitjà stated, 3 years after the initial MDA, two cases of macrolide resistance were identified, which spread to three other cases at month 42. That gave a total of five confirmed cases; the same phenomenon with three confirmed cases occurred in other MDA programme in another region of Papua New Guinea 3 years later.

One person who received 1.5 g of azithromycin (dose calculated according to weight) was still infected 6 months later, according to yaws serology, and also developed new papillomatous lesions at multiple sites in the body, showing that the bacteria had not been eliminated. After molecular identification, the strain was seen to be the same one, but that in the interim it had developed a mutation (A2059G) that required treatment with parenteral penicillin.

When whole genome sequencing was performed, it was possible to see that genetic changes in all five cases were located in the same genomic region. That meant that a single strain had spread to all. This mutation spread to siblings, school friends and play mates.

Dr Mitjà's conclusion was that selection of resistance – while not common in his studies – can occur following MDA. Most important, he stated, was that this resistance can spread to others, meaning that this could compromise an eradication programme based on azithromycin MDA. His recommendations, therefore, included:

- careful monitoring of clinical and biological surveillance of yaws, especially in MDA programmes;
- ensuring clinical cure means to conduct a second visit after 14 days of treatment;
- identifying whether or not there is treatment failure;
- management of macrolide resistant yaws patients with benzylpenicillin treatment to achieve cure and to avoid dissemination of resistant strains; and
- ensuring biological surveillance means to continue with detection of drug resistance systems through the strengthening of capacities of laboratory networks in endemic countries where some of those detected specimens can be sent to a reference laboratory for drug resistance testing.

He also recommended proposing alternative regimens for macrolide resistance post-MDA detected cases, along with researching new drugs and drug combinations.

### 5.3 Trachoma

The presentation on antimicrobial resistance in trachoma treatment was given by Dr Catherine Oldenburg, Assistant Professor and Infectious Disease Epidemiologist at the Francis Proctor Foundation of the University of California in San Francisco.

Dr Oldenburg talked not only about antimicrobial resistance after azithromycin MDA for trachoma but also on azithromycin distribution to combat child mortality.

Azithromycin MDA, Dr Oldenburg began, is used in several different conditions, including yaws (see above) as well as in trachoma, and more recently in generalised efforts to reduce child mortality.

In trachoma elimination programmes, entire populations are treated on an annual basis with doses of 20 milligrams per kilogram of body weight, up to a maximum adult dose of one gram.

Some communities have been treated in this way for over a decade and, despite repeated treatment, there are communities that continue to have non-negligible prevalences of active trachoma. In response to this, one question has been to ask if there is emergent macrolide resistance in the causative organism of trachoma, *Chlamydia trachomatis*.

Detection of resistance in *C. trachomatis* is relatively difficult. There have been a handful of studies in ocular isolates and these have not found evidence of macrolide resistance; there was no evidence of macrolide-resistant strains in a recent study in Amhara, Ethiopia, in communities which have received multiple years of azithromycin MDA.

However, it was stated that as azithromycin is a broad-spectrum antibiotic, there is potential for bystander effects where resistance may occur in organisms that are not the intended target.

Dr Oldenburg gave attention to the results of a systematic review led by Dr Kiran O'Brian, an epidemiologist at the Proctor Foundation, published in 2018.

Antimicrobial resistance in *Streptococcus pneumoniae* is commonly evaluated after azithromycin MDA and has been carried out in multiple studies. Generally, Dr Oldenburg summarized, one tends to see, at the population level, a short-term increase in the prevalence of resistance in pneumococcus following azithromycin MDA, followed by a decline in the prevalence of resistance after MDA has been discontinued and selection pressure removed. As such, the frequency of azithromycin distribution affected the prevalence of pneumococcal resistance in communities. Problems of resistance increase as the frequency of distribution increases. The systematic review also identified evidence of increased resistance selection in other organisms, including *E. coli*, *Staphylococcus aureus*. (There was no evidence of resistance in a recent study of *Mycoplasma genitalium*; this was not included in the systematic review as it has only recently been published.)

More recently, azithromycin MDA has been considered for use in programmes for prevention of child mortality in high mortality settings. This, Dr Oldenburg stated, is different from the MDA used in trachoma.

One study on the use of azithromycin to prevent child mortality (MORDOR) in three countries in sub-Saharan Africa (Malawi, Niger and the United Republic of Tanzania) showed that azithromycin MDA for children aged 1-59 months significantly reduced all-cause mortality in this age group. In the Niger study site, 30 communities that participated in MORDOR received 48 months of either biannual azithromycin MDA or placebo. Rectal samples were collected in children in these communities to evaluate for genetic resistance determinants. Analysis used whole genome sequencing to evaluate genetic resistance determinants present in the stool. There was evidence of emergence of significant resistance to macrolides: a sevenfold increase in macrolide resistance in commensal bacteria of children receiving azithromycin compared with those receiving placebo.

In the case of resistance to beta-lactams, there is some indication that children in azithromycin-treated communities have increased prevalence of resistance compared with children in placebo communities. Confidence intervals are relatively wide, but the analysis seemed to show some evidence that there could be resistance to other antibiotic classes in children in the azithromycin communities too.

Dr Oldenburg then raised a lingering question about the clinical impact of resistance after azithromycin MDA. In explaining the context of the question, she stated that macrolides are not the most commonly used antibiotic class in communities in which azithromycin MDA is indicated either for trachoma or for child mortality reduction. But azithromycin remains an important first-line treatment for many common infectious diseases; understanding conclusions and the clinical implications of resistance is therefore important.

Ongoing analysis of data from the MORDOR trial, Dr Oldenburg said, has not indicated a decrease in efficacy over time with regard to childhood mortality. In concluding her presentation, Dr Oldenburg noted the following priorities for monitoring antimicrobial resistance after azithromycin distribution:

- continued monitoring of *C. trachomatis*, including monitoring with new genetic techniques;
- understanding the relative impact of targeting distribution – to children only, for example, compared with treating an entire community; and
- continued monitoring for decreased efficacy of antibiotics following cessation of azithromycin MDA.

## Discussion

The discussion following Dr Oldenburg's presentation addressed the issue of azithromycin resistance as recounted in both Dr Oldenburg and Dr Mitjà's presentations.

The first question centred on how best to ensure that resistance to azithromycin does not become widespread, given the medicine's importance in yaws eradication efforts and other MDA campaigns.

Dr Mitjà recognized the importance of this point, noting that WHO is currently implementing guidelines for the administration of azithromycin to treat and eradicate yaws in multiple communities in remote areas. He was of the opinion that those programmes would need to consider how they are going to monitor treatment failures. Whenever a case of treatment failure is identified, ideally that person should be treated with an alternative regimen while, if at all feasible, swab collection for PCR testing and macrolide resistance detection could be done in the event that resistance is identified and the whole community should receive alternative treatment with penicillin.

To a question about new drug development studies to ensure future availability of alternatives to azithromycin, Dr Mitjà agreed that this was very important, noting that azithromycin treatment had developed as an alternative to penicillin, being easier to administer in remote regions. A readiness to develop further options was imperative, however, he stated, adding that work with the University of Washington (Seattle, USA) and on the search for new molecules was ongoing. At this point, he said, lymecycline would appear to be a good alternative.

Dr Oldenburg addressed a question about azithromycin MDA as a possible intervention to combat child mortality in African countries, and subsequent effects on antimicrobial resistance, compared with impacts observed in trachoma elimination programmes. She stated that that one notable difference between MDA for child mortality compared with that for trachoma might be that MDA for childhood mortality is focused only on a very small subset of the population, namely children aged under 5 years, whereas azithromycin for trachoma is given to every individual aged over 6 months in a given population. There may be potential for reduced selection for resistance, Dr Oldenburg said, when targeting only a very small subset of the population. However, there have not been head-to-head comparisons or head-to-head studies yet which allow for adequate comparison, so there cannot be any certainty in this regard. Studies are ongoing also to evaluate spill-over effects on resistance in children or in people not in the 1–59-month age range for azithromycin distribution to combat child mortality. One interesting next step, she suggested, would be to understand whether selecting for resistance in children also confers resistance in bacteria in people not treated as part of the MDA. The hope is, she continued, that by treating a subset of the population you select for less resistance in the community, but as of yet, that has not been confirmed.

## 5.4 Visceral leishmaniasis

Turning to parasitic diseases, the moderator Professor Mas-Coma invited Professor Shyam Sundar to present on antimicrobial resistance in treatment of visceral leishmaniasis. This disease, he began, has three big foci: one in Brazil, another in Africa (affecting Ethiopia, Kenya, South Sudan, Sudan and Uganda) and the third and formerly biggest focus in South-East Asia (including Bangladesh, India and Nepal). However, with declining incidence following the elimination programme in South-East Asia, the eastern Africa sub-region has become the biggest focus.

He began by saying that in the past, pentavalent antimonials were the only medicines used to treat visceral leishmaniasis. In the Indian subcontinent, initially, the dose used was 10 mg per kg, administered over a period of 6-10 days. Dose and duration were subsequently increased when a decline in efficacy was observed. Following reports that not every patient was responding to treatment, the duration of treatment was increased from 6 to 10 days to 20 days in 1980, with a corresponding cure rate of 96%. Then, in 1988, 40 days of 20 mg antimonial per kg was seen to cure 97% of patients.

Professor Sundar then described a study that he and his team conducted in which three groups were randomized: one to antimony alone; the second to antimony with gamma interferon for 30 days; and the third to gamma interferon for 15 days. Results showed that cardiotoxicity occurred in a significant number of patients and there were four deaths. Final cure rates were also far from satisfactory – the best results were seen in group 2 – at some 49%.

Subsequently, another study was conducted to test what might be happening in a larger number of patients. Antimonials were given for 30 days at a rate of 20 mg per kg and 209 patients were treated. Here, treatment failure was observed in 95 patients – some 50%. The initial cure rate was 42.6% after completion of treatment parasites were examined. Finally, after clinical and parasitological analysis, there were also 14 relapses, which led to a final cure rate of only 35%, which was very disappointing.

Clearly, treatment efficacy has reduced over the years. In order to evaluate contributing factors, a survey of 312 patients was conducted, showing that initially 73% of patients went to local healers; only 27% went to a qualified medical practitioner. With regard to regularity of treatment, some 58% took a regular treatment and 42% irregular treatment. Duration of treatment was again incomplete in almost 50% of the patients, meaning that in the end, only 26% patients had adequate dose and duration of treatment; this was considered to have played an important role in the development of drug resistance to antimonials.

Pentamidine was then used as a second treatment for a short period, but quickly showed declining efficacy and following further years in which cure rates steadily declined. The Government of India in 1999 called an expert committee meeting at which it was decided that in those areas where more than 10% drug resistance was occurring in patients with visceral leishmaniasis, amphotericin B deoxycholate would be used.

This, according to Professor Sundar, was easier said than done, however, because its use was restricted only to hospitals, requiring a patient to be hospitalized for 5-6 weeks. There was also very high incidence of drug-related adverse events. Clinical and laboratory surveillance was required, and the treatment was also very expensive both in human and economic terms. The treatment, therefore, could not be deployed in the majority of health facilities and was actually not used extensively during this time.

Following this, miltefosine emerged as a treatment, and was to be the basis for a programme to eliminate visceral leishmaniasis in Bangladesh, India and Nepal, instituted in 2005 for elimination by 2015. This target was not met, however, and the next target for elimination has been set for 2023.

Professor Sundar noted, however, that there were also big problems with miltefosine, including a long treatment period, potential teratogenicity, a long half-life leading to threats of emerging resistance, a rate of serious adverse events of some 2%, as well as a recent study which showed a doubling of relapse rates from 3% to 6% after a decade of use. Again, use of this medicine was discontinued.



The upshot of all these trials, Professor Sundar noted, was the need for new (oral) antileishmanial medicines, regimens of short duration, directly-observed therapies and, potentially, a combination of two or more medicines. Unfortunately, he added, the medicines in question are freely available over the counter in India, which has knock-on effects if the desire is to prevent resistance.

He noted in conclusion that combinations of medicines actually led to very high cure rates: liposomal amphotericin B plus miltefosine for 7 days gave cure rates of 98.7%, as did liposomal amphotericin B plus paromomycin for 10 days and miltefosine plus paromomycin for 10 days.

## Discussion

The ensuing discussion opened with a question about the best practice advice to national leishmaniasis control programmes in prevention of antimicrobial resistance in treatment for visceral leishmaniasis.

Professor Sundar replied that programmes are currently dependent upon only one unaffordable medicine. He reiterated his belief that there needs to be a combination of available medicines. These can be recommended, but unfortunately might not be uniformly implemented due to non-availability and other factors. Prevention of drug resistance, therefore, ought to be managed through the use of the correct and most effective regimen.

Multidrug therapy appears to be the way to prevent development of resistance, Professor Sundar said, reiterating also that availability of treatments without prescription should be eliminated so that effective medicines are not available for misuse.

A subsequent question centred on recommendations to stakeholders, particularly researchers, for the monitoring of antimicrobial resistance in treatment for visceral leishmaniasis. Professor Sundar replied that looking carefully at the cure rate of different regimens, the observation of declines in cure rates could be a first sign of the development of drug resistance. For antimonials, extensive monitoring should be carried out, he reiterated, reminding the meeting also of the need for new medicines, preferably in oral combination.

## 6. Monitoring drug efficacy in preventive chemotherapy medicines

Professor Bruno Levecke was invited to present his work on monitoring drug efficacy in preventive chemotherapy medicines, with a particular focus on intestinal worm and soil-transmitted helminth infections.

He began with some context, noting that school-based MDA is a cornerstone of current efforts to control morbidity from these diseases. Depending on prevalence, populations are treated twice a year, once a year or not at all. They are treated with one of two medicines principally – albendazole or mebendazole – which are kindly provided by the original manufacturers. Coverage over time, from 2008 and 2018, has increased significantly, multiplying by four during that decade.

Why, therefore, does one monitor drug efficacy? Professor Levecke explained that this is done for two reasons: first, while recognizing the invaluable role of these medicines in combating the effects of soil-transmitted helminth infections, it might also be the case that selection for anthelmintic resistance is also occurring. This is a real threat because, despite the fact that two different medicines are used, both belong to the same pharmaceutical family and have the same mode of action for killing the worms. The bottom line, therefore, is that they amount to one drug treatment. On top of that, they are administered in a single oral dose, which is not always 100% efficacious, and it is likely too that underdosing is happening on a large scale. Secondly, there are very few alternatives. If anthelmintic resistance emerges in the current context, there is no real alternative medicines or combinations of medicines that might be implemented.

Referring to Dr Argaw Dagne's opening remarks, Professor Levecke noted the ambition to set up a surveillance system to monitor drug efficacy and the emergence of antimicrobial resistance globally.

With the support of WHO, and the financial support of key partners, he said, it has been possible not only to draft a study protocol with significant detail,<sup>1</sup> but also to pilot this protocol.

This monitoring system consists of three steps:

- **Step 1: country selection, based on:**
  - the PCT WHO database (from the past 5 years);
  - the median national coverage of school-aged children > 50%; and
  - the availability of subnational coverage data.
- **Step 2: selection of an implementation unit, based on:**
  - coverage of > 90%; and
  - consideration of other aspects, including recent prevalence data, presence of sentinel schools and accessibility to schools and laboratory facilities.

Professor Levecke confirmed that countries and areas within countries where coverage had been very high for a long period of time should be considered.

- **Step 3: a field study** involving analysis of stool samples using standard microscopic methods. After 21 days and further testing it is possible to determine the efficacy of the medicine.

The study has also preserved stool samples for further molecular analysis in the future. As yet, there is no validated marker of antimicrobial resistance; therefore, further research is required.

Thus far, efficacy results are available for Bangladesh, Cambodia, Lao People's Democratic Republic and Viet Nam. Studies in Rwanda and Senegal are pending (interrupted as a result of COVID-19). Studies in Burundi, Cameroon, Ethiopia, India, Myanmar, the Philippines, Togo and the United Republic of Tanzania were planned for 2020.

The upshot of this analysis, said Professor Levecke, is that the results to date, for both albendazole and mebendazole, show efficacy against *Ascaris* and *Trichuris* to be satisfactory. Efficacy for hookworms was reduced in Cambodia and Lao People's Democratic Republic, and was doubtful in Viet Nam. Potential factors to explain this reduced efficacy are being evaluated before it can be claimed that any treatment failure has occurred.

Professor Levecke summarized his presentation with the following key messages.

- The emergence of drug resistance in treatment for soil-transmitted helminthiases is likely given high coverage rates and the prospect of continued donations of medicines.
- The surveillance system has been pilot tested and is being implemented.
- Potential factors other than anthelmintic resistance need to be excluded.
- Markers of resistance in human helminthiases are still not yet validated.
- Revision of the 2013 WHO guidelines is ongoing.

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\* Assessing the efficacy of anthelmintic drugs against schistosomiasis and soil-transmitted helminthiases. Geneva: World Health Organization; 2013 (<https://www.who.int/publications/i/item/9789241564557>).

## Discussion

The discussion began with a question about the WHO manual for assessing the efficacy of albendazole and praziquantel, developed 10 years ago, and the possible need for a new efficacy assessment.

Professor Levecke replied that there is indeed a need to revise some aspects put forward as well as to prepare individual guidelines. For instance, he said, additional support could be required around the question of which diagnostic methods to use, and also around the interpretation and reporting of data. At this point in time, he noted, only point estimates are being reported, rather than the variations observed across the data. These may be small changes, Professor Levecke concluded, but it is time to revise and update documents.

## 7. Antimicrobial resistance in trematode treatment

The meeting's final presentation was given by the moderator Professor Mas-Coma himself.

Beginning with some context, Professor Mas-Coma stated that trematodes causing human disease include *Fasciola hepatica* and *F. gigantica*, with *F. hepatica* being distributed worldwide and *F. gigantica* restricted to certain parts of Africa and Asia. Both are liver flukes and follow a two-host life cycle in freshwater transmission.

Currently, only one medicine – triclabendazole – is effective against both migrating juvenile and adult flukes. Triclabendazole is administered orally, postprandially, and has excellent clinical tolerability, being useful even in the treatment of early postnatally infected infants. It is particularly efficient in hospitalized patients – two doses of 10 mg/kg show very high cure rates and only very, very rarely is there a need for a third dose.

For preventive chemotherapy, 10 mg/kg doses are being administered once a year for the main purpose of reducing morbidity. Alternative treatments are available but are not as effective; these include nitazoxanide and albendazole. Fascioliasis is the only trematodiasis not responding appropriately to praziquantel treatments.

WHO reached an agreement with Novartis many years ago on a donation programme for triclabendazole, which allowed for a worldwide control strategy against fascioliasis. The strategy began in four countries and was very successful, encountering no great problems with side-effects and thus allowing the programme to expand progressively.

On the specific question of resistance to triclabendazole, Professor Mas-Coma summarized the situation as follows.

- The mode of action of triclabendazole is not known.
- There is an absence of markers for resistance to triclabendazole.
- Present knowledge about triclabendazole suggests that:
  - resistance originates in animals;
  - resistance reported in humans always occurs in areas where there is resistance in animals;
  - there are no data suggesting that triclabendazole resistance spreads geographically; and
  - there are problems with the uncontrolled manufacturing of generics.

## 7.1 One Health complementary control intervention

Professor Mas-Coma then outlined a proposal that the preventive chemotherapy intervention be complemented by a One Health complementary control intervention.

Crucial aspects to be considered in the design of this One Health intervention included the following:

- the complexity of interacting factors between humans, domestic reservoirs, sylvatic reservoirs, lymnaeid snail vectors, the environment and climate;
- the wide heterogeneity of transmission patterns and epidemiological situations according to human endemic areas in different countries and continents;
- the need for a multidisciplinary field and experimental studies; and
- the need for a sufficient baseline of knowledge and data.

He stated that the Northern Bolivian Altiplano human hyperendemic areas had been selected for the following reasons<sup>1</sup>:

- presence of only one *Fasciola* species as a causal agent and one snail species as an intermediate host;
- highest human prevalence and intensities reported;
- multidisciplinary key knowledge already available;
- 10 years of preventive chemotherapy by yearly one-dose treatment campaigns;
- infection and reinfection of children detected in interannual monitoring;
- background of high endemicity maintained by infection rates in livestock; and
- a One Health action would decrease human infection risk.

The ultimate purpose of this intervention, according to Professor Mas-Coma, would be that the One Health action guideline be applicable to other human endemic areas. For the following reasons:

- sheep and cattle should be considered priority within the One Health action
  - for management measures to decrease infection
  - for appropriate treatments of infected animals to decrease field contamination and lymnaeid infection rates; and
  - for treatment of these animals with drugs other than triclabendazole, such as closantel, to avoid the emergence of potential resistance.

## 7.2 One Health challenges and considerations

Professor Mas-Coma stated a need to work both experimentally and in the field. It was further stated that global warming has allowed snails to spread, widening their geographical distribution. This means that present geographically endemic areas are expanding.

The other aspect, added Professor Mas-Coma, was livestock, which is why there is now a One Health focus on field studies and experimental studies; he then spoke of the need to push forward, in the sense that there is a need to implement easily feasible measures. He cited the construction of fences around fresh-water reservoirs as an example.

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\* Mas-Coma S, Buchon P, Funatsu IR, Angles R, Artigas P, Valero MA, et al. Sheep and cattle reservoirs in the highest human fascioliasis hyperendemic area: experimental transmission capacity, field epidemiology, and control within a One Health initiative in Bolivia. *Front Vet Sci.* 2020 (<https://www.frontiersin.org/articles/10.3389/fvets.2020.583204/full#h10>, accessed 19 March 2021).

On the human and biomedical components of complementary control by One Health intervention, Professor Mas-Coma noted that field studies would consider:

- an assessment of human infection sources;
- outdoor defecation practices;
- improvement of indoor toilet and latrines connected to outdoor freshwater sources; and
- other behavioural aspects linked to transmission and analysis of pathological markers.

Experimental studies in this regard, he said, would include an assessment of human participation in liver fluke transmission as well as the need to know whether preventive chemotherapy might induce resistance.

### 7.3 One Health feasibility and conclusion

On whether a One Health intervention would be feasible, Professor Mas-Coma stated his opinion that it would, but that there would be many difficulties in putting it in place. There would also need to be appropriate monitoring of results, affordable and controllable activities, an ability to evaluate the efficiency of control measures and a need to verify that successful measures in the pilot zone could be extended to the rest of the endemic area.

Difficulties in considering other subsequent human endemic areas might then include the coexistence of two or more snail species, he said. This is usual in Latin America and parts of Africa and Asia, but confusion between host and non-host species can lead to confusion in the field, as can the co-existence of *F. hepatica* and *F. gigantica* species in the same endemic area. This occurs in parts of Africa and Asia, Professor Mas-Coma added.

His conclusion, therefore, was that a One Health intervention would be feasible but that a combination of field and experimental studies would be needed to assess its effectiveness, as well as long-term funding. There would also be a need to consider appropriate monitoring of the results of prioritized One Health actions, which is usually not affordable in large human endemic areas.

Scaling up of multipronged control interventions may be resources intense and complex but feasible.

## 8. General discussion

The meeting was then opened to questions from participants, both on general or topics not covered by specific presentations and on topics directly arising from invited speakers' presentations.

Dr Argaw Dagne fielded a question about the type of recommendations that might be provided for the use of ivermectin widely used recently in the context of COVID-19 but originally used as an antiparasitic medicine.

The answer to this question stated that there is no evidence that ivermectin is effective for the treatment of COVID-19 or SARS-CoV-2 infection. WHO, it was emphasized, does not recommend use of ivermectin for any other treatment than that recommended in national programmes. It was further recommended that national programmes and drug regulatory authorities undertake strict monitoring of the use and distribution of ivermectin. For the time being, therefore, use of ivermectin for COVID-19 treatment could not be recommended, nor for that matter for any other use other than that indicated for treatment of NTDs.

A subsequent question turned to the matter of antiparasitic resistance, definition and cut-off. Generally, the meeting was told, antiparasitic resistance is defined as the genetic ability of parasites to survive treatment with antiparasitic treatments that have generally been effective against those parasites in the past. The same applies to antibiotic resistance or antiviral or antifungal resistance.

There followed a question about young people and their engagement in the field of antimicrobial resistance. The panellists were asked about their recommendations to ensure young people have a place in the fight against antimicrobial resistance for treatment of NTDs as a way of securing a generation that is free from these diseases.

Respondents felt that younger people ought to be actively encouraged to join the fight against NTDs and the antimicrobial resistance movement, noting that they had vital contributions to make in raising awareness and in using their networks, including social media and other innovative communication methods, to disseminate messages. Professor Cambau added as a qualification to this that it was also important to retain the memory of what has happened in the past. As was shown in the meeting's presentations, the first effect of antimonial treatment, for example, is efficacy, which makes researchers happy. It was only a few years later, he noted, that resistance emerged. She stressed therefore the need for patience and to keep in mind what has previously been done – which means working with older people sometimes too!

A question was addressed then to Professor Sundar about the relationship between the appearance of resistance in the medicines used to treat visceral leishmaniasis and the more or less zoonotic transmission characteristics of other leishmaniasis species. He replied that this aspect had yet to be studied but that he suspected there would be an observable relationship.

This closed the discussion section of the webinar.

## 9. Closing remarks

Thanks and closing comments were given by Dr Mwelecele Ntuli Malecela, Director, WHO Department of Control of Neglected Tropical Diseases. Dr Malecela thanked Professor Mas-Coma for his guidance and moderation before widening her thanks to include all the meeting's presenters and all colleagues able to join and participate.

The webinar had taken place, Dr Malecela said, in the context of the launch of the One Health Global Leaders Group on Antimicrobial Resistance, raising engagement on antimicrobial resistance to a very high political level, combining interest from the political and advocacy realms as well as the technical points of view.

World Antibiotic Resistance Awareness Week, Dr Malecela said, was an excellent fit with the NTD context given that the NTD community was well used to dealing with a large range of pathogens that include viruses, bacteria, parasites and fungi. Perhaps no other department, she said, handles such a variety of antimicrobials in treating such a diverse group of infections. It was her privilege, therefore, to participate in this discussion. NTD treatments have reached more than a billion people for the fifth successive year, including mass treatments and also individual treatments, and this has exceeded expectations.

Dr Malecela added that although morbidity and mortality have been reduced, the discussion about antimicrobial resistance is a reminder of the need for continued vigilance in order to generate awareness about best practices, which can then be shared not only with policy-makers and health workers but also with the general public, to minimize and avoid the spread of antimicrobial resistance.

This vast topic, of course, requires a series of debates and deliberation, but today constituted an excellent beginning, Dr Malecela said, referencing presentations on basic principles, best practices, the One Health approach and key messages for selected NTDs. The scope of the One Health approach calls for closer collaboration with a wide range of stakeholders, such as the Food and Agriculture Organization of the United Nations and the World Organisation for Animal Health, as the threat of antimicrobial resistance emerges from multiple factors in the overuse of antimicrobials.

In the spirit of the new NTD road map, Dr Malecela commented, working across departments internally and cross-sectorally, the WHO Department of Control of Neglected Tropical Diseases is now the anchor department for zoonoses and will continue to work alongside the WHO Global Coordination and Partnership department for Antimicrobial Resistance.

Finally, she said, the decision to broaden the scope of the antimicrobial resistance movement beyond antibiotics to include antifungals and antiparasitics was most welcome.

Dr Malecela emphasized the importance of maintaining antibiotic arsenals for treatment, noting that many treatments rely entirely on one or two medicines. She reiterated the warning, "Handle with care," noting the meeting's insistence on strengthening well-established drug efficacy studies in NTDs, as well as resistance monitoring and surveillance, including laboratory networks.

## Annex. Agenda

Time	Topic	Speaker
14:00–14:05	Welcome and introductory remarks	Dr Haileyesus Getahun
14:05–14:15	Overview of antimicrobial use and resistance against NTDs	Dr Daniel Argaw Dagne
14:15–14:30	Antimicrobial resistance monitoring in leprosy treatment	Professor Emmanuelle Cambau
14:30–15:00	The threat of azithromycin resistance emergence: what are the needs to prevent and monitor azithromycin resistance for yaws eradication and trachoma elimination programmes?	Dr Oriol Mitjà Dr Catherine Oldenburg
15:00–15:15	Antimicrobial resistance in visceral leishmaniasis treatment	Professor Shyam Sundar
15:15–15:30	Monitoring of drug efficacy in preventive chemotherapy medicines: contribution to potential drug resistance monitoring	Professor Bruno Levecke
15:30–15:45	Preventing antimicrobial resistance by promoting the One Health approach: the case of <i>Fasciola</i> and resistance to triclabendazole	Professor Santiago Mas-Coma
15:45–15:55	Final discussion and conclusion	Professor Santiago Mas-Coma
15:55–16:00	Closing remarks	Dr Mwelecele Ntuli Malecela





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