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Monitoring the efficacy of drugs for neglected tropical diseases controlled by preventive chemotherapy

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Abstract

In the last decade, pharmaceutical companies, governments and global health organisations under the leadership of the World Health Organization (WHO) have pledged large-scale donations of anthelmintic drugs, including ivermectin (IVM), praziquantel (PZQ), albendazole (ALB) and mebendazole (MEB). This worldwide scale-up in drug donations calls for strong monitoring systems to detect any changes in anthelmintic drug efficacy. This review reports on the outcome of the WHO Global Working Group on Monitoring of Neglected Tropical Diseases Drug Efficacy, which consists of three subgroups: (i) soil-transmitted helminthiases (ALB and MEB); (ii) onchocerciasis and lymphatic filariasis (IVM); and (iii) schistosomiasis (PZQ). Progress of ongoing work, challenges and research needs for each of the four main drugs used in helminthic preventive chemotherapy (PC) are reported, laying the ground for appropriate implementation of drug efficacy monitoring programmes under the co-ordination and guidelines of the WHO. Best practices for monitoring drug efficacy should be made available and capacity built as an integral part of neglected tropical disease (NTD) programme monitoring. Development of a disease-specific model to predict the impact of PC programmes, to detect outliers and to solicit responses is essential. Research studies on genetic polymorphisms in relation to low-efficacy phenotypes should be carried out to identify markers of putative resistance against all NTD drugs and ultimately to develop diagnostic assays. Development of combination and co-administration of NTD drugs as well as of new drug entities to boost the armamentarium of the few drugs available for NTD control and elimination should be pursued in parallel.

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1 Introduction

Neglected tropical diseases (NTDs) such as lymphatic filariasis, onchocerciasis, schistosomiasis and soil-transmitted helminthiases remain major public health problems in many parts of the world. The global strategy aimed at reducing morbidity and transmission of these helminth infections is preventive chemotherapy (PC), the large-scale periodical administration of anthelmintic drugs to population groups at risk [1]. In the last few years, these PC programmes have received growing political and scientific attention. The World Health Organization (WHO) has laid down a roadmap to guide implementation of the policies and strategies set out in the Global Plan to Combat NTDs 2008–2015 [2]. More than 70 pharmaceutical companies, governments and global health organisations have committed to support the implementation of this roadmap in the London Declaration on NTDs [3] by sustaining or expanding existing drug donation programmes, with the support of the Bill & Melinda Gates Foundation (B&MGF) and bilateral agencies such as the US Agency for International Development (USAID) and the UK Department for International Development (DFID), under the leadership and coordination of the WHO. Such large involvement of the pharmaceutical industries has led to recent pledges and donations of anthelmintic drugs including ivermectin (IVM), praziquantel (PZQ), albendazole (ALB) and mebendazole (MEB). In 2013 alone, 718 million people at risk have been treated with more than 1.3 billion tablets of anthelmintics in the context of PC [4]. This worldwide scale-up in drug donations re-enforces the necessity for thoroughly designed monitoring systems that allow early and accurate detection of any changes in drug efficacy that may arise through the evolution of anthelmintic drug resistance in these parasites [5]. Monitoring drug efficacy is therefore of paramount importance in control programmes based on PC and will become even more important for the challenge of the correct use of anthelmintics (dosage, frequency, combinations) and to ensure the implementation of successful mitigation strategies [6,7]. At present, however, the efficacy of NTD drugs is poorly monitored, mainly due to the absence of a framework that guides PC programme managers in how to assess drug efficacy.

Therefore, in 2010 the WHO's Strategic and Technical Advisory Group for NTDs (STAG) founded a Working Group on monitoring the efficacy of drugs for NTDs controlled by PC. The central aim of this working group was to provide practical recommendations on monitoring drug efficacy that will fit into the routine monitoring and evaluation (M&E) of a PC programme for NTD control/elimination in endemic countries and consists of three subgroups focusing on: (i) onchocerciasis and lymphatic filariasis (IVM); (ii)soil-transmitted helminthiases (ALB and MEB); and (iii) schistosomiasis(PZQ).Here we report on the progress of ongoing work, challenges andresearch needs for each of the four main drugs used in helminthic PC (ALB, MEB, PZQ and IVM) and lay the ground for appropriate implementation of drug efficacy monitoring programmes under the co-ordination and guidelines of the WHO.

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2 Ivermectin

2.1 Progress of ongoing work

2.1.1 Onchocerciasis

2.1.1.1 Tools for measuring ivermectin efficacy: IVM is used to reduce transmission of Onchocerca volvulus and the morbidity associated with the presence of microfilariae (mf). IVM acts to eliminate existing mf and to prevent production of new mf for an extended period of time, potentially breaking the transmission cycle at the level of mf uptake by the blackfly vector. Any reduction in IVM efficacy could be manifested either as a reduced microfilaricidal effect or a reduced antifecundity effect on the adult worms. It has been noticed in some communities and individual hosts that the skin may repopulate with mf more rapidly than had been previously observed, leading to concerns of suboptimal responses to IVM that could be indicative of developing resistance to IVM. Evaluation of response to IVM treatment has traditionally depended on skin snip assessment pretreatment and at different times after treatment. The microfilaricidal effect of IVM is maximal at ca. 30 days after treatment. However, to assess the antifecundity effect of IVM, skin snips (1 mg of skin) need to be taken at different times after treatment [90 days (optimal time) up to 180 days]. Skin snip biopsy is painful and, for ethical and practical reasons, needs to be limited in frequency. Mf counting in skin snip samples is challenging for efficacy monitoring, especially when mf counts are low as control programmes approach elimination. Recently, quantitative PCR has been employed on skin snip samples to detect the presence of O. volvulus infection [8]. Depending on when the skin snip is taken in relation to IVM treatment, this method could provide indirect evidence regarding the efficacy of IVM treatment. However, the direct ability to detect populations of O. volvulus that are less responsive to IVM has been a goal of monitoring for responsiveness to IVM in recent years. The development of a predictive model called ONCHOSIM has helped the African Programme for Onchocerciasis Control (APOC) to monitor IVM response in sentinel sites [9].

2.1.1.2 Identification of markers for monitoring of suboptimal ivermectin response: In response to concerns about possible suboptimal response to IVM, seven laboratories, in Australia, Burkina Faso, Cameroon, Canada, Ghana, France and the UK, have been collaborating since 2011 with the overall objective to determine any highly significant genetic difference between suboptimal responder and good responder worm populations in order to obtain the best unbiased marker for IVM resistance. The specific objectives were: (i) identification of potential genetic markers for suboptimal response to IVM in O. volvulus; (ii) identification of potential markers of gene flow for predicting possible spread of genotypes with low susceptibility to IVM; (iii) development of a diagnostic tool for use by control programmes for surveillance of emerging suboptimal responder strains; and (iv) capacity building in Cameroon, Ghana and Burkina Faso.

Since commencement of the work, the O. volvulus genome has become available. Based on O. volvulus genome differences between IVM-naïve communities and communities with ‘good’ and ‘poor’ response to periodic IVM treatment, 800 single nucleotide polymorphisms (SNPs) were initially identified as potential markers of resistance. This set of SNPs has been

further narrowed to 160 SNPs. Further research has been undertaken to measure the response to IVM treatment in human populations with different IVM treatment histories in Cameroon. Differences were observed in mf repopulation rates and embryograms between a population that had been repeatedly treated with IVM and a treatment-naïve population [10,11]. The research questions are: (i) whether these indications of reduced efficacy in Ghana and Cameroon do represent a reduction in the previously observed efficacy to IVM; (ii) whether similar indications of reduced efficacy may be occurring in other endemic areas; and (iii) whether this may impair the performance of the Onchocerciasis Control Programme.

2.1.1.3 Sample repository: The sample repository consists of samples collected in areas differing in level of endemicity, habitat (forest versus savannah), vectors and history of IVM treatment (no treatment versus >10 treatments). Currently, a total of 3334 samples are archived at the Multi Disease Surveillance Centre (MDSC) laboratory in Burkina Faso.

2.1.1.4 Epidemiological evaluation: Epidemiological assessment has been considered as a proxy indicator for efficacy of IVM on onchocerciasis in the absence of a molecular marker. Epidemiological data have been collected in 22 foci (304 villages, 76,390 persons) in nine different countries. The epidemiological evaluations for phase 1a indicated that sites examined in Burundi,Cameroon, Central African Republic, Democratic Republic of Congo (DRC) and Nigeria are progressing towards elimination. The epidemiological evaluation for phase 1b indicated that treatment can be stopped in sites examined in Ethiopia, Guinea and Tanzania, but not in Malawi (due to bordering countries where onchocerciasis is still present) and some sites in Nigeria.

2.1.1.5 In-depth situational analysis of sites with unsatisfactory results: In total, seven sites in DRC, Nigeria and Cameroon did not progress as anticipated by the ONCHOSIM model. For these sites, APOC has set up an independent group of in-country experts to conduct a situational analysis.

2.1.2 Lymphatic filariasis (LF)—Two fundamental questions are still to be answered: how to monitor drug efficacy during mass drug administration (MDA); and how to test for reduced efficacy against lymphatic filariasis.

2.1.2.1 How to monitor drug efficacy during mass drug administration: Resources (grant ‘Filling the gap’ from the B&MGF, at the NTD Modelling Consortium) are now available for modelling to predict the progress after MDA, and hence possibly suggesting reduced drug efficacy, retrospectively, if progress is unsatisfactory (cf. ONCHOSIM). WHO data from LF sentinels sites could be used to model expected declines in mf prevalence following MDA.

2.1.2.2 How to test for reduced efficacy against lymphatic filariasis: At present, no tools are available and any reduction in efficacy may be detected if progress towards elimination is less than expected, taking into account issues such as compliance.

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The WHO protocol for assessing drug efficacy against soil transmitted helminths (STHs), as part of the LF elimination effort, can be employed in STH Transmission Assessment Survey settings [12]. For LF, sentinel and spot-check sites may serve the same purpose.

2.2 Challenges and future research needs

2.2.1 Onchocerciasis

2.2.1.1 Identification of markers for monitoring of suboptimal ivermectin response: Due to budget constraints, the number of parasites to be genotyped will be reduced and the phenotypic characterisation of possible suboptimal response has only been conducted on a restricted sample in Ghana and Cameroon. Thus, the number of well characterised samples for genotyping is less than satisfactory. Further validation with a limited number of the most significant SNPs on male worms and mf at different time points after IVM administration collected during studies in Cameroon and Ghana should be carried out and confirmed on field samples from other countries. Finally, further reduction in the number of marker SNPs to four to eight would allow these final SNPs to be validated as potential response markers. In addition, training, technology transfer and capacity building should continue.

2.2.1.2 Continuation of sample repository and epidemiological evaluation: Archiving of parasite samples and epidemiological evaluations in sentinel sites should continue, including entomological surveys. In-depth situational analysis of sites where the progress based on ONCHOSIM was unsatisfactory should be conducted. To this end, in 2015 a software programme will become available with maps and endemicity levels, allowing countries to compare their onchocerciasis endemicity and trends towards elimination. Suboptimal response should be distinct between reduced efficacy and the tail of a normal response. Endemic countries should be aware that IVM is still a very effective drug, while monitoring for continued good efficacy of IVM is important. A standard protocol to assess IVM efficacy for onchocerciasis and to define an acceptable threshold for cure and suppression of microfilarial repopulation is needed.

2.2.1.3 Development of moxidectin: Phase 1, 2 and 3 studies have been conducted with moxidectin being compared against IVM for onchocerciasis control. In these studies, moxidectin was superior to IVM, supressing mf numbers for _18 months. These very favourable results justify the registration of moxidectin for use against onchocerciasis. Use of moxidectin would significantly reduce the time to elimination of onchocerciasis [13] and also simplify the task of monitoring IVM efficacy, which is variable depending on when samples are taken.

2.2.2 Lymphatic filariasis

2.2.2.1 Monitoring drug efficacy: Three pending questions need answering: (i) what is the community Loa loa prevalence at which LF MDA can be safely administered; (ii) can models be validated with field data and used to determine where drug efficacy is less than expected; and (iii) can risk maps be used as the basis for stratifying surveillance requirements. A predictive model based on data from the WHO should be developed. Eventually, the model should be available also for diethylcarbamazine.

2.2.2.2 Assessment of drug efficacy: An appropriate protocol adequately powered to assess drug efficacy in sentinel and spot-check sites should be defined, as a significantly higher number of infected subjects are required in sentinel sites.

2.2.2.3 Lymphatic filariasis and onchocerciasis efforts to monitor drug efficacy should be merged: LF and onchocerciasis efforts to monitor drug efficacy should be merged, especially after the restructure of APOC beyond 2015. A group of experts on LF, under the leadership of the WHO, should interact closely with APOC to explore how to best integrate LF monitoring.

3 Albendazole and mebendazole

3.1 Progress of ongoing work

3.1.1 Assessment of drug efficacy—The drug efficacy of single-dose MEB 500 mg (J&J) and single-dose ALB 400 mg (GSK) against soil-transmitted helminths (STHs) was evaluated in two multicentric efficacy trials. The results revealed a high efficacy, measured by egg reduction rate (ERR), of both drugs against Ascaris lumbricoides (>95%) and a lower efficacy against Trichuris trichiura (ca. 65%). For hookworms, ALB resulted in a significantly higher ERR (ca. 96%) compared with MEB (ca. 80%). The efficacies reported by ERR decreased as a function of increasing infection intensity for MEB (A. lumbricoides) and ALB (T. trichiura) [14,15]. It is well known that anthelmintics are not 100% effective after a single treatment [1] against some helminths (e.g. ALB against trichuriasis or MEB against hookworm infection). However, when these drugs are administered periodically they are extremely effective in cutting down the worm burden (i.e. eliminating morbidity) and in some cases even in reducing transmission [16,17].

3.1.2 Coprological techniques—To date, various coprological techniques have been applied to detect and quantify STH infections, including Kato–Katz, Mini- FLOTAC, FLOTAC and McMaster [18]. Evaluation of coprological techniques mainly focuses on sensitivity. However, it remains unclear whether this is a prerequisite. A meta-analysis comparing prevalence and intensity of infection, cure rate (CR) and ERR based on collection of one or two stool samples processed with single or duplicate Kato–Katz thick smears reported that the accuracy of prevalence estimates and CR was lowest with the minimal sampling effort, but that this was not the case for estimating infection intensity and ERR [19]. Hence, a single Kato–Katz thick smear is sufficient for reporting infection intensity and ERR following drug treatment. These results are also in favour of pooling stool samples to ease stool collection and to reduce workload in surveys [20]. In veterinary parasitology, the FECPAKG2 diagnostic system has been recently developed and preliminary studies in Ethiopia showed that its application for human STHs is promising. The FECPAKG2 system would enable: (i) to perform egg counts without any use of a microscope; (ii) to ultimately automate faecal egg counts; and (iii) to submit results from remote locations via the Internet for analysis, interpretation, reporting and linking to expertise, and hence eliminating the need for a microscope or highly skilled technicians/clinicians in the field [21,22].

3.1.3 Standard protocol for assessing anthelmintic drug efficacy—As an outcome of Sections 3.1.1 and 3.1.2 above, the group developed a standard protocol for assessing anthelmintic drug efficacy against STHs and schistosomiasis [23], with standard sample size, laboratory techniques, interval between baseline and follow-up surveys, and statistical analysis of the data collected. One of the main features of the protocol is the indication of a unique indicator, the ERR, based on the group-based arithmetic mean for the evaluation of anthelmintic drug efficacy [24].

3.1.4 Morbidity indicator parameters—Monitoring morbidity is important to assess impact. However, assessing morbidity caused by STHs is difficult as the few morbidity indicators (growth, anaemia) are not specific. Faced with the same diagnostic challenges, researchers in veterinary parasitology have recently moved from stool examination towards serology-based assays to gain more insight into morbidity of helminths. Of these serology-based assays, the SERASCA1 test is probably the most promising for human application. This antibody enzyme-linked immunosorbent assay (ELISA) test allows the detection of infections both of immature and adult Ascaris worms in pigs. Both experimental and field studies indicated that the SERASCA1 test is more sensitive compared with stool examination and it correlates significantly with the daily growth of the animals [25].

3.1.5 Tutorials—Tutorials for operational procedures for NTD control programmes have been developed and made available on YouTube (https://www.youtube.com/watch?v=q_yfdtE3TSE) and are now also embedded in the website of the Global Atlas of Helminth Infections. A standard version of the faecal parasitological methods is being produced and updated by the Department of Control of NTD at WHO and will be available through standard tutorials.

3.1.6 Short- and long-term monitoring—Short-term monitoring (=assessment of drug efficacy) is essential to detect any emergence of anthelmintic resistance. However, currently the efficacy of drugs is poorly monitored. It is recommended that this should become an obligation for NTD control programmes based on PC (every 4 years). Long-term monitoring (=assessment of prevalence/infection intensity) allows evaluating and adjusting the MDA strategy. PC programmes are solely based on the frequency of drug administration. A recent study in Jimma (Ethiopia), however, indicated that there are seasonal differences in STH infections, hence suggesting that the yearly seasonality may also need to be considered to further improve the impact of MDA (Mekonnen, unpublished data).

3.1.7 Reporting of drug efficacy—There is a need to strive for a global reporting system on the web in which the following information can be accessed: (i) where are the regions at risk; (ii) where are the drugs distributed; (iii) where are the drugs failing; and (iv) what are the potential confounding factors. The global digital revolution could play a role by data collection through mobile phones.

3.1.8 Alternatives for benzimidazoles (BZs)—Papaya cysteine proteinases (CPs) are known to have anthelmintic properties both in animals and humans. However, up-to-date efficacy data are lacking. An efficacy trial assessing the efficacy of a single oral dose of

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ALB and CPs against two levels of Trichuris suis infections in pigs indicated a higher reduction both in egg and adult worm counts for CPs compared with ALB [26].

3.1.9 Monitoring and evaluation—A Markov chain model to ring the bell for monitoring long-term progress has been developed. This model mimics the ONCHOSIM model and predicts reduction in prevalence and intensity for each species of STH over time by a given coverage of PC [27,28]. A software programme to assist programme managers in predicting the impact of STH control programme efficacy is under evaluation.

3.2 Challenges and future research needs

The challenges for BZ efficacy monitoring and the future research need to fill the gap are summarised below.

3.2.1 Standardised protocols and diagnostics—Recent guidelines on assessment of drug efficacy should be implemented in the field in sentinel countries. WHO tutorials for standard operational procedures on diagnostic methods and on the organisation of surveys and laboratory work should be developed. FECPAKG2 should be modified towards a field-friendly tool, and other diagnostics based on mobile phone application should be developed and tested. The SERASCA1 test should be assessed to differentiate between patent/past infections and to evaluate its correlation with morbidity parameters in the human population.

3.2.2 Drug trials and development of new products—Following BZ multicentric trials, oxantel/pyrantel and levami-sole should be obtained to perform large-scale efficacy trials. In light of recent evidence of increased efficacy of drug combinations, combo products without BZ drugs (i.e. tribendimidine and moxidectin) need to be tested to expand the drug armamentarium and to serve as back-up in case resistance to BZs should emerge [29]. The possibility to take papaya CPs towards human application should be explored.

3.2.3 Mathematical modelling and data management—The Markov chain model should be tested and evaluated and the software from the WHO made available. The methodology of pooling samples for drug efficacy monitoring is promising [20] but should be further evaluated. Data on drug efficacy should be increasingly captured using palmar tool and digital platforms.

4 Praziquantel

4.1 Progress of ongoing work

4.1.1 Monitoring drug efficacy—A multicentric (Brazil, Cameroon, Ethiopia, Mali, Tanzania and The Philippines) drug efficacy study of PZQ against Schistosoma spp. is ongoing, aimed at assessing the efficacy of a single oral dose of 40 mg/kg PZQ against schistosomiasis on ERR (arithmetic mean) in school children. Secondary objectives are to understand the potential role of novel zoonotic hybrids and animal reservoirs in maintaining infections within human hosts despite large-scale PC. Whilst drug efficacy can be measured as a population average effect, as is standard practice within the veterinary medicine fields, this impedes assessment of the variation among individuals caused by measurable (fixed)

and immeasurable factors (random factors, e.g. drug underlying resistance/tolerance of parasites). As one potential solution for this issue, at least in terms of the statistical analyses of PC data sets, a random mixed model has recently been developed aimed at capturing both sources of variation, allowing identification of individual suboptimal/atypical responses through comparing against a 'reference' distribution of 'normal' responses using data from naïve populations [30]. Another potential solution is to perform individual host and parasite sampling and analyses aimed to assess the impact of PC on PZQ efficacy. In one recent study at the individual host level, point-of-care circulating cathodic antigen (POC-CCA) tests and multiple Kato–Katz smears were compared in Schistosoma mansoni drug efficacy studies following repeated rounds of PZQ PC. This study was conducted in Uganda amongst primary-school children who had received between zero and eight past rounds of PZQ treatment. This study indicated that six Kato–Katz smears (two per stool from three stools) and/or one POC-CCA test was required for accurate M&E or drug efficacy studies in areas under long-term PZQ PC. Although unable to quantify ERRs, one POC-CCA test appeared to be more sensitive than six Kato–Katz smears both at 4 weeks post- PZQ and 6 months post-PZQ [31]. Notably, a POC-CAA assay has been demonstrated to detect single worm infections [32] and hence has the potential to become an ideal diagnostic test, particularly in areas targeted for 'elimination of schistosomiasis as a public health problem'. Furthermore, the POC-CAA test has the potential to detect infection in either serum or urine (and potentially also saliva), thereby enhancing its applicability within future PC programmes, when cost and accessibility become feasible.

4.1.2 Schistosome genetics and genomics—Development of biomarkers in relation to PZQ efficacy has also made recent progress. These range from simple non-invasive in vitro phenotypic assays of miracidial responses [33], to population genetic studies in relation to PC [34], and genomic studies revealing the species-specific drug action of oxamniquine in schistosomes [35]. Next-generation sequencing (NGS) aimed at identifying recent selective pressures on S. mansoni in response to PZQ are currently underway, including work with both whole-genome sequencing [36] and exome sequencing [37] methodologies. For the latter NGS technique, only the protein-coding sequences are captured and sequenced, thus reducing the S. mansoni genome from 380 Mb to 15 Mb [38]. Exome sequencing has already been used successfully to identify oxamniquine resistance genes in S. mansoni [37]. Following the initial publication of the draft Schistosoma haematobium genome [39], similar research on characterising PZQ PC selection pressures on the causative agent of urogenital schistosomiasis in sub-Saharan Africa is now also planned. Although the cost of NGS has fallen exponentially in recent years, the outlay of sequencing all 380 Mb of the schistosome genome remains, nevertheless, currently beyond the financial capacity of most institutions. When dealing with a disease that affects the very poorest in the world, the most useful public health interventions are those that cost the least and are broadly sustainable; therefore, it is important that this technology is targeted to answer the most relevant public health questions [40].

4.1.3 Mechanism of drug resistance—The molecular responses of Schistosoma japonicum to PZQ were evaluated by a transcriptional and functional approach [41,42]. Numbers of differentially expressed genes between males and females following exposure to

PZQ were found and more genes were changed in female schistosomes. It can be speculated that PZQ may kill males more readily than females [41]. The potential impact is that female worms remain alive after treatment and egg production temporarily ceases giving a false indication of ERR/CR until male worms re-appear. Furthermore, analysis revealed differential gene expression for the calcium-signalling pathway: the serine/threonine-specific protein kinase that is regulated by the Ca2+/calmodulin complex (CaMKII) is upregulated in response to PZQ. If CaMKII transcription was reduced, the IC50 dosage (drug concentration that inhibits 50% of the parasites) of PZQ increased. CaMKII mitigates the effect of PZQ, probably through stabilising Ca2+ fluxes within parasite muscles and the tegument [41]. In addition, multidrug resistance (MDR) transporters may be important for fine-tuning schistosome drug susceptibility. For example, inhibition or knock-down of MDR transporters potentiate PZQ effects on motility both of juvenile and adult schistosomes [42].

4.1.4 Animal reservoirs—Drug resistance is not the only explanation for apparent treatment failures. One may simply be low MDA coverage and compliance issues, another is natural tolerance and/or rapid transmission, including the potential role of additional animal reservoirs. Many NTDs are zoonotic, i.e. diseases that can be transmitted, directly or indirectly, from animals to humans. Schistosoma japonicum remains endemic in China despite five decades of multifaceted interventions including PC, molluscicide, health education, sanitation and environmental improvement, and has re-emerged in some areas where it was thought to have been eliminated. Spill-over from animal reservoirs appears to be maintaining such human schistosomiasis through a combination of bovine livestock and, as recently identified, rodent wildlife, depending on the habitat type [43,44]. The finding that rodents can act as a major S. japonicum infection reservoir poses particular challenges for PC given the notorious logistical difficulties in achieving rodent control itself. Similar challenges are presented in The Philippines, where parasitological and molecular analyses have revealed dogs to be partially responsible for maintaining transmission and subsequent human infections despite human PC [45]. The potential for ongoing transmission through zoonotic reservoirs is not the reserve only of the Asian NTDs, as modern molecular diagnostic techniques are beginning to reveal. Non-human primates, rodents and insectivores are responsible for human S. mansoni infections in some regions of Africa and the Caribbean. Furthermore, whilst S. haematobium was believed to be essentially an exclusively human-specific parasite, recent molecular studies have confirmed bidirectional hybridisation between S. haematobium with the animal (cattle, goat and sheep) schistosome species Schistosoma bovis and Schistosoma curassoni amongst infected children in West Africa [46]. The implications of zoonotic hybrids on transmission potential are substantial, particularly in terms of the potential for increased definitive and intermediate host ranges, hybrid vigour, as well as any potential differential PZQ susceptibilities [46]. Fortunately, the first major new research programme aimed to elucidate the evolutionary dynamics and epidemiology of such novel zoonotic hybrids in sub-Saharan Africa is now underway [47].

4.1.5 Mathematical modelling—Use of mathematical models aimed at understanding schistosomiasis transmission dynamics and improving the ability to control or even eliminate infection are increasingly becoming available. For example, recent developments of Markov models [48], full age spectrum transmission models (NTD Modelling

Consortium) (http://www.ntdmodelling.org/about), and force of infection (FOI) models [49] have all recently been published. Furthermore, accurately parameterised mathematical models incorporating genetic or genomic data can, for example, inform on rates of change of schistosome phenotypes or genotypes associated with drug resistance, so that M&E studies can understand what, where and when they need to monitor, as well as advise on optimal treatment strategies to maximise the gains from limited resources [40].

4.1.6 Drug development—The drug oxamniquine is currently only active against S. mansoni. Oxamniquine is activated in schistosomes by sulfotransferase, after which the activated oxamniquine binds the DNA. This is the first mode of action of a human anthelmintic drug to be defined. To make oxamniquine efficacious against other schistosomes, the crystal structures of the enzyme–drug–cofactor complex for S. mansoni, S. haematobium and S. japonicum have been compared [35]. From these crystallographic analyses, analogues of oxamniquine were derived and were subsequently screened in high-throughput assays for efficacy. The most efficacious compounds will be screened in an in vivo assay of interactions between oxamniquine and sulfotransferases from all three human species of schistosomes [35].

4.2 Challenges and future research needs

4.2.1 Monitoring drug efficacy—Many subjects remain egg-positive several weeks post-treatment. The biological mechanism for this needs further attention, in particular when POC-CAA is brought into assessment of drug efficacy and/or M&E.

4.2.2 Monitoring and evaluation—It would be important to unravel the causes and consequences of hybrids, especially for different susceptibilities to PZQ, and to evaluate whether it is possible to control (eliminate) zoonotic schistosome infections in Africa (cf. S. japonicum in Asia).

4.2.3 Mathematical modelling—The currently available Markov, mixed random and FOI mathematical models aimed to assess drug efficacy should be completed and expanded to other helminths, including Schistosoma spp.

4.2.4 Resistance biomarkers—Biomarkers to identify potential for drug resistance to oxamniquine and PZQ should be further investigated.

5 Conclusions

A few cross-cutting issues have been identified to enhance the monitoring of drug efficacy in NTD control programmes.

Capacity building is an area to invest, and specific training to monitor drug efficacy at programme and supranational laboratory level should be pursued. Linked to this, supranational reference laboratories for NTDs in Africa, Asia and Latin America should be identified, and ring testing of in vivo and in vitro standard assays should be established. Standard operating procedures and best practices for monitoring drug efficacy should be made available and disseminated as an integral part of NTD programme monitoring. In

endemic countries, special attention should be given in building capacity to implement PC programmes and to set up efficient monitoring systems, including for drug efficacy. The development of a disease-specific mathematical model to predict the impact of PC programmes, to detect outliers and to solicit responses is of utmost importance. Co-ordination of epidemiologists working on this topic would allow knowledge sharing and improved synergies in order to come up with a unique tool. Research studies on genetic polymorphisms in relation to low-efficacy phenotypes should be carried out in order to identify markers of putative resistance against all NTD drugs and ultimately develop diagnostic assays. It is crucial to allow sensitive markers to be used ultimately on isolates from the field to refine the monitoring system, which is still based on direct and relatively insensitive methods. An important operational research line, which is ongoing parallel to the monitoring of drug efficacy, is the development of combination and co-administration of NTD drugs as well as the development of new drug entities that will add to the armamentarium of the few drugs available for NTD control and elimination [29]. All of these efforts are likely to be successful if implementing partners are well co-ordinated through agencies such as the WHO, and sensitised on best practices of efficacy monitoring.

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