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Commentary

Cure rate is not a valid indicator for assessing drug efficacy and impact of preventive chemotherapy interventions against schistosomiasis and soil-transmitted helminthiasis

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ABSTRACT

Every year in endemic countries, several million individuals are given anthelminthic drugs in the context of preventive chemotherapy programmes for morbidity control of schistosomiasis and soil-transmitted helminthiasis. The capacity to evaluate accurately the efficacy of the drugs used as well as the health impact produced by treatment is of utmost importance for appropriate planning and implementation of these interventions. Cure rate is an indicator of drug efficacy that was originally developed for assessing the clinical efficacy of antibiotics on selected bacterial diseases. Over time, this indicator has also been widely applied to anthelminthic drugs and consequently used to monitor and evaluate preventive chemotherapy interventions. In the author's opinion, however, measurement of cure rate provides information of limited usefulness in the context of helminth control programmes. The present article analyses the peculiarities of helminth infections and those of the drugs used in preventive chemotherapy, explaining the reasons why the cure rate is not an adequate indicator in this specific public health context.

1. Introduction

Currently, most evaluations of the efficacy of anthelminthic drugs on soil-transmitted helminths (STH)[1] and schistosomiasis[2] are based on analysis of cure rate (CR) calculated as the percentage of infected individuals at baseline who are free from infection after treatment. CR is an efficient indicator of drug efficacy against bacterial diseases, and researchers in the field of helminthiasis adopted CR for analogy. However, in the author's opinion, this indicator is less efficient for helminth infections.

2. Peculiarities of schistosomiasis and soil-transmitted helminthiasis

Schistosomes and STHs do not replicate in the human host; if few parasites survive treatment, these remain few. This is different from most other communicable diseases in which, if few infectious agents survive treatment, they replicate, restoring the initial pathology.[3]

Another peculiarity is that morbidity associated with STHs and schistosomes is proportional to the number of parasites. When several hundreds of parasites infect the host, morbidity is severe; a drastic reduction in the number of parasites results in a improvement in morbidity because the few surviving worms cause only minimal harm.[3]

A third characteristic is that the number of worms per person is not distributed evenly: most individuals have infections of light or moderate intensity, while few harbour infections of high intensity.[4]

The main objective of preventive chemotherapy (PC) against schistosomes and STHs is therefore to eliminate the infections of moderate and heavy intensity, with the aim of preventing morbidity.[3]

3. Why cure rate is not a valid indicator for assessing drug efficacy and the impact of preventive chemotherapy interventions

As a consequence of the characteristics of schistosomes and STHs and the peculiarities of PC detailed above, the author has identified the following reasons that limit the

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usefulness of CR as a tool to monitor drug efficacy as well as the impact of PC against these diseases.

3.1. Cure rate is influenced by the intensity of infection at baseline

In endemic areas, some individuals with schistosomiasis or soil-transmitted helminthiasis are infected by few worms and some with hundreds of worms. It is intuitively easier to cure an individual infected with few worms; therefore, CR after treatment will be more satisfactory in areas where high-intensity infections are rarer.[1]

It is therefore inappropriate to compare CRs calculated in areas with different proportions of infections of high/low intensity: as an example, albendazole has a relatively low CR (45%) against hookworms when the mean pre-treatment infection intensity is high [1120 eggs per gram of faeces (EPG)],[5] and a high CR (83%) when the faecal egg count at baseline is lower (174 EPG).[6]

3.2. Cure rate is influenced by the sensitivity of the parasitological method used to recover eggs from stool

The more sensitive the parasitological method used to recover eggs in stool, the lower will be the CR.

The sensitivity of a parasitological technique is a function of the intensity of infection[7] and of the intrinsic capacity of the technique to recover parasite eggs from specimens. The number of negative readings (and consequently the CR after treatment) is, by definition, lower when a sensitive technique is used. Use of the Kato–Katz technique that, compared with other methods, lacks sensitivity at low infection intensities[8] will result in a better CR.

3.3. Cure rate cannot be considered as a proxy for 'morbidity reduction', the objective of preventive chemotherapy

CR measures the number of infected individuals who are completely cured after treatment. For this reason, a drug that reduces by 90% the number of worms infecting a given individual results in the same CR (0%) as a completely inactive drug. However, whilst in the first case the effect on morbidity will be massive, in the second it will be irrelevant.

3.4. Cure rate does not take into consideration that preventive chemotherapy is applied periodically

CR, measured by definition at a single point after treatment, makes no allowance for the long-term nature of PC, which also achieves cure of target individuals as a result of its periodical application.

The following two examples, one from Vietnam and the other from Cambodia, refer to PC interventions conducted with drugs with a low CR and show that reduction in prevalence of infection was in fact achieved after a number of rounds of PC.

Figure 1 presents the impact on hookworm infections (CR = 59–81%)[1] produced by the administration

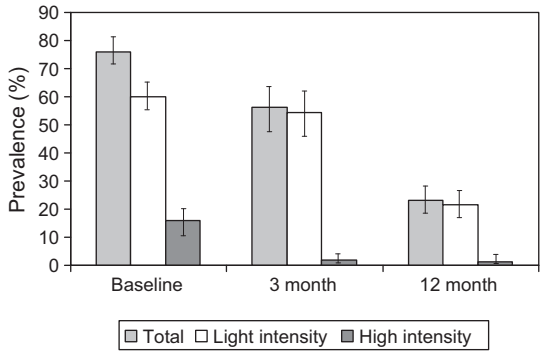

Figure 1. Reduction in total prevalence of hookworm infections and prevalence of light- and high-intensity infections during the 1-year implementation of a preventive chemotherapy campaign in Yen Bai Province, Vietnam.[9] Error bars indicate the 95% confidence intervals.

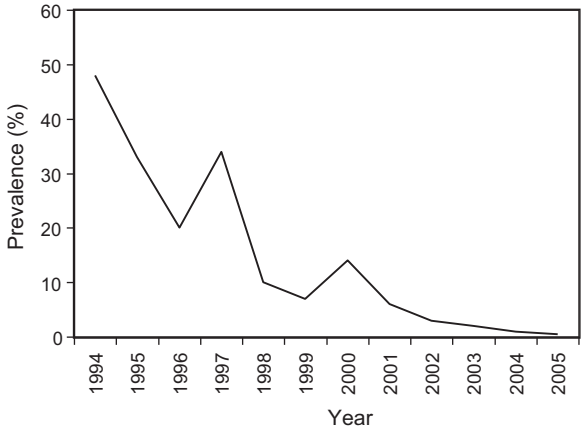

Figure 2. Reduction in the prevalence of *Schistosoma mekongi* infections during the preventive chemotherapy campaign conducted for 10 years in Stung Treng and Kratie Provinces, Cambodia.[11]

of albendazole to 52 000 women in Yen Bai Province, Vietnam.[9] Parasitological data were collected from a sample of 360 women. After the first round of PC the prevalence of hookworm infection decreased from 75% to 60% (20% reduction or CR), whilst the prevalence of hookworm infections of high intensity declined from 15% to 2% (87% reduction). The second round produced a reduction in prevalence from 60% to 22% (63% reduction) and a complete elimination of infections of high intensity.

Figure 2 presents the effect of the annual distribution of praziquantel on *Schistosoma mekongi* (CR = 60%)[10] in a population of 80 000 individuals conducted for 10 years in Cambodia. Data were collected in a sample of over 1500 individuals. In this case, the number of infections has progressively been reduced until no infections were identified by survey in 2006.[11]

4. Conclusions

In the author's opinion, the examples presented in this article show that CR has a limited capacity to provide conclusive information on the efficacy of anthelminthic drugs in different areas (because differences in the baseline

situation influence the results) or with different laboratory techniques (because the CR results depend strongly on the sensitivity of the parasitological method used). In addition, CR is not suitable to assess the impact produced by PC as it does not measure the main objective of such an intervention (i.e. reduction in morbidity consequent to a reduced intensity of infection). This opinion is confirmed by the excellent performances obtained by PC interventions with drugs for which the CR is considered low. For all these reasons, in the author's view the role of CR in the context of helminth control programmes should be reconsidered.

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