Synchronized and regular deworming of children and women in South Africa : policy and practice

Synchronized and regular deworming of children and women in South Africa: policy and practice

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SOUTH AFRICA IS A SIGNATORY TO WORLD Health Assembly (WHA) resolution 54.19 (May 2001), which calls for regular, synchronized treatment of helminthiasis in developing countries, particularly where the prevalence of worm infestation exceeds 50%. Helminthic infection is usually a hallmark of poverty and reasons why it should be controlled in disadvantaged communities are compelling. However, existing South African legislation regulating the procurement and use of anthelmintic medicines effectively renders group-based deworming as agreed to by WHA member states, and endorsed by the South African minister of health, non-implementable in practice. In order to make deworming sustainable, low-cost, unregistered anthelmintics must be imported from international procurement agencies. At present, this is not permitted. Another problem is that both medical and non-medical personnel are confused by out-of-date information in package-inserts regarding safety for young children and pregnant women. Albendazole and praziquantel should be de-scheduled and ivermectin, levamisole and possibly nitazoxanide should be registered in a way that permits treatment by non-medical personnel. Rational alternation of medication is important because reliance on mebendazole will lead to resistance. All batches of anthelmintics ought to comply with pharmacological quality specifications and testing should be routine. Facilities for doing this are available in South Africa.

International policy

In May 2001, the South African minister of health endorsed World Health Assembly (WHA) resolution 54.19, which calls for regular, synchronized treatment of helminthiasis in high-risk groups when the prevalence is 50% or more.[1–3] Member states are urged to sustain control as a public health measure and ensure access to essential drugs. It is proposed that in communities where the prevalence of worm infestation is excessive, treatment programmes should reach 75–100% of school-age children by 2010, as well as other important groups such as preschool children and young women. These objectives are based on the fact that regular treatment is the quickest way to alleviate most of the huge burden of disease caused by infection with worms in categories of people predisposed to infestation. A key aspect is that treatment should be simultaneous for all children in a school. This will reduce overall morbidity, be of direct benefit to treated individuals and have an advantageous epidemiological effect by reducing the number of worm eggs shed into the environment.

The WHA call for action came in a decade within which a lot of information on infection of South African children by intestinal worms and protozoa has been published.[4–32] These data confirm that a widespread problem exists, and there are reasons why the situation may be deteriorating. A serious deficiency is that worm infestation in young women has not been studied. In KwaZulu-Natal (KZN), Limpopo and Mpumalanga provinces, as well as in neighbouring states, schistosomiasis and hookworm infection can occur together in women of child-bearing age and children.

While our main purpose is to assess key South African aspects relating to implementation of WHA resolution 54.19 on control of worm infestation, the current and emerging threat posed by pathogenic intestinal protozoa must be recognized.[2,33]

Background to the WHA resolution

Globally, it is children and women in particular who carry the greatest burden of disease resulting from helminthiasis.[1–3] It has been estimated that the loss in disability-adjusted life years caused by intestinal parasites is second only to tuberculosis (TB) and exceeds that due to malaria.[2] Infection by soil-transmitted helminths, schistosomes and cestodes can, either alone or in combination, impair health, growth, nutrition, learning and physical performance.[1–3,34–44] Damage to vital organs and even the fetus, may be serious and is sometimes irreversible. Notably, a meta-analysis of randomized controlled trials has reported a mean weight gain of either 0.24 kg or 0.38 kg per child, depending on the model used, after a single treatment with any anthelmintic.[37] This amounts to a massive effect over a large number of children, which should be cumulative if treatment starts at an early age and is repeated regularly. It is the kind of result that would be a strong, long-term investment in health. Lastly, urogenital schistosomiasis may be facilitating HIV infection by increasing contact between blood, inflammatory cells and the virus in semen and vaginal secretions.[39]

For epidemiological and immunological reasons,[2,20,45–48] regular, blanket deworming could affect diseases that are co-endemic with worm infestation in different ways. Minimization of long-term contact with helminthic antigens by sustained deworming may, in theory, facilitate immunological protection against HIV/AIDS and TB, but in doing so might increase susceptibility to allergies and/or autoimmune diseases.[20,32,45] The position regarding atopic disorders is controversial. In Cape Town, exposure to *Ascaris* has been associated with exacerbation of allergic asthma in a specific ethnic group, according to reports published in 1979 and 1988.[47,48] Research completed in 2004 has confirmed this finding (C.C. Obihara, unpubl. data). On balance, the potentially beneficial results of regular deworming should outweigh any that are detrimental. For example, when immunological activation caused by intestinal parasites is sustained, some vaccines are less effective, including bacille Calmette-Guérin vaccine against TB and oral cholera vaccine.[45] For the same reason, trials of some potential anti-HIV vaccines may fail or give misleading results.[46] Since worm infestation is so widespread, regular, synchronized deworming, especially of children before sexual activity starts, may be an economical way to minimize impairment of vaccine trials, and might also eventually make immunization more effective. Furthermore, countering the immune response to parasitic worms may or may not result in slower disease progression after infection by HIV or *Mycobacterium tuberculosis*.[32,45,49]

A powerful demonstration of the demand for deworming and of informed consent in the African context is when children who do not attend school run to get treatment, as they have been seen

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to do in Cape Town, before temporary facilities close or the tablets are finished. Some of these children are not in school because they are AIDS orphans. Africans have probably always known that worm infestation is a serious problem. There are traditional deworming remedies, generally derived from plants that have medicinal properties. However, indigenous people never lived at a population density of 34 000 per km^2 in shacks at ground level, as in parts of Sites B and C in Khayelitsha, Cape Town, and other informal settlements, before they started migrating to cities and towns in search of work and health care.[12,20,24] Neither traditional African medicine nor conventional health services can cope with the new situation. Yet under these conditions synchronized, school-based deworming can be a powerful overall health catalyst, as has been shown by operational research in Khayelitsha.[12] When children pass large *Ascaris* worms soon after treatment with a single tablet, it generates confidence in participatory health care. One small, 8-year-old girl passed 52 of these worms the first time she was treated. It is highly significant that children want and strive to get treatment. They need to experience our response to their call for help as being direct, rapid and effective.

Implementation of WHA resolution 54.19 in South Africa

Given the compelling reasons why infestation by intestinal parasites should be controlled, and with South Africa having supported international policy that calls for regular, group-based deworming of children and women living in poverty, the question arises as to whether we can deliver on deworming in our own country. The short answer is that we cannot, for more than one reason.

Only one anthelmintic can be used at present

The Medicines and Related Substances Control Act (No. 101 of 1965), as partially amended by the Medicines and Related Substances Control Amendment Act (No. 90 of 1997; subsequently referred to as 'the Act'), is inadvertently preventing implementation of WHA resolution 54.19 in South Africa by restricting the use of deworming medicines through the requirements for registration, scheduling and dispensing. Only mebendazole (a benzimidazole) has the potential to be used, subject to limitations on dispensing, because it is a Schedule 1 (S1) medicine. Reliance on a single anthelmintic (i.e. mebendazole) would be bad practice because there is potential for development of resistance.[1,2,50,51] To reduce this risk, non-benzimidazoles such as ivermectin and levamisole could be used alternately with benzimidazoles, but they are not registered in this country. Ivermectin is also effective against skin parasites such as scabies mites and jigger fleas, both of which are known to cause problems in South Africa.

Other essential anthelmintics for group-based therapy are albendazole and praziquantel but they are Schedule 4 (S4) medicines. This means that they can be used legally only under prescription for treatment of individuals. There have been millions of safe treatments with both of these anthelmintics around the globe for many years.[1–3,50–55] Albendazole is the drug of choice against hookworm that occurs in parts of South Africa, Mozambique and Zimbabwe.[5,8,18,21,27,28] These parasites are one cause of anaemia, low iron status and growth stunting because they feed on blood obtained by biting into the intestinal surface, with release of hydrolytic enzymes and anticoagulant that promote bleeding.[43] Praziquantel is needed to treat schistosomiasis (bilharzia), a disease which can cause serious damage to various organs, including the spinal cord and fetus.[1–3,18,29,52,54,55] Schistosomiasis is present in five South African provinces (especially KZN) and all neighbouring states except Lesotho.[18,22] Praziquantel is also effective against tapeworms and soil-transmitted helminths, and is used in the treatment of cysticercosis and hydatid disease.

Nitazoxanide (Alinia®, Romark Laboratories) is a relatively new compound that is effective against intestinal worms as well as some protozoa and bacteria.[51,56] On the basis of studies that have found it to be efficacious and safe, it should be assessed for possible registration in South Africa for use in both group-based and individual therapy.

Restrictions on the use of anthelmintics

The Act does not authorize non-medical personnel to treat with scheduled medicines. Even in the S1 category, there are limitations that have the potential to block treatment by the teachers, environmental health officers (EHOs), community health-workers, parents, NGO personnel and other lay volunteers who must participate directly if implementation of WHA resolution 54.19 is to be achieved. It is essential that non-medical personnel carry out treatment and manage programmes because the health service does not have sufficient resources to cope with seriously competing health priorities.[1,3,9,12] For example, in research projects conducted since 1996 in the southwestern Cape, there have been almost 200 000 treatments with mebendazole that were carried out mostly by teachers, and sometimes by EHOs, after initial training by school nurses.[12–14,20,24,32] It was usually the schools that obtained informed consent and teachers who completed treatment registers. No adverse reactions to treatment have been reported. This scale of school-based delivery on a regular basis would not be sustainable by the health service working alone. Teachers have also treated children in a deworming project in Mpumalanga province.[18] Broad-based health partnerships are the only way to implement and sustain deworming programmes in terms of human resources and cost-effectiveness. It is particularly important to have the education service and community structures as active partners.[9,12,40,41]

Legislation and the Medicines Control Council

The Medicines Control Council (MCC) has a key role to play in the development of school-based deworming because it controls the use of registered and unregistered drugs in South Africa. In contrast, traditional medicines are not controlled and unregistered substances are used on a large scale. While the MCC is responsible to the public for the safety and pharmaceutical quality of medicine, it should be equally obliged to facilitate service delivery of affordable essential drugs to people living in poverty. A serious problem is that recent amendments to legislation concerning the scheduling, prescription and dispensing of drugs are blocking implementation of school-based deworming, which has been endorsed by the South African minister of health and is the only effective way to reach most children. The new legal restrictions inadvertently violate the right of children to receive regular anthelmintic treatment at school. Consequently, adjustments to the amendments are necessary as a matter of urgency in order to allow deworming to take place in schools under the supervision of school nurses. With regard to authorization for the use of affordable unregistered medicine, Section 21 of the Act appears to be focused mainly on individual emergencies, such as chemotherapy in semi-terminal cases of cancer. Exemption from Section 36 of the Act could permit the conditional use of unregistered anthelmintic. It remains to be determined whether the MCC will

grant such an exemption. To get imported mebendazole registered as an alternative strategy might take as long as two years, for various reasons.

Cost of deworming tablets, packaging, labelling and package-inserts

In order to make deworming programmes affordable for developing countries, international procurement agencies have been established to cut costs (for instance, see: www.ida.nl). Market research has shown that single-dose mebendazole tablets from an offshore source would have cost less than 25 South African cents per tablet delivered in Cape Town in 2004, including value-added tax and transport expenses. These tablets are bulk-packed, often at 500 per container. The lowest possible price (government tender) for an equivalent tablet registered in this country was R1.58 per tablet (single-packed) in September 2004, which is 632% of the offshore price. Other (non-tender) South African mebendazole tablets were quoted at R3.10 and R6.00 per tablet in 2004, which are respectively 1240% and 2400% of the offshore price. Each single-packed, South African tablet carries the cost of a cardboard box decorated with printing and patterns in colour, a blister or foil pack inside the box (with more printing on it), and a package-insert. The packaging, printing and insert combined may cost more than the tablet. Furthermore, unpacking a tablet to treat a child becomes a slow process compared to accessing a bulk supply of loose tablets, and the discarded packing amounts to a lot of waste for disposal. This situation is not compatible with a quick, efficient, school-based operation.

Outdated information about treatment of young children and pregnant women

The package-inserts for the brands of mebendazole that are marketed in South Africa, contain warnings on use in pregnancy and for children under two years of age. These differ from new findings and recommendations concerning safety.[1,3,36,52–55] The incorrect warnings confuse medical and non-medical personnel and have impeded, and sometimes blocked, development and implementation of group-based deworming. New data on safety during pregnancy (after the first trimester) come mainly from deworming of thousands of women with mebendazole in Sri Lanka and Sierra Leone, because of infestation by hookworm. The prevalence of these parasites is higher in adults than in children and they are a cause of low iron status and anaemia, both of which can have serious consequences for the mother and the baby. In treated women, iron status improved, anaemia was reduced and there were no deleterious effects in terms of birth outcome.[1,3] It is also safe to use praziquantel to treat schistosomiasis in pregnant women.[1,51,54,55]

There is increasing evidence that young, pre-school children need to be dewormed and that it is safe to give them benzimidazoles and praziquantel.[1–3,36,53] In South Africa in 2000 and 2001, studies involving hundreds of young children (including neonates) in Durban and at Hlabisa in northern KZN showed that more than 90% can be infected by worms. These surveys also revealed that the protozoon *Giardia duodenalis,* which is a cause of diarrhoea, can be common.[10,16] In 2003, the Medical Research Council of South Africa (MRC) was commissioned to determine the prevalence of worm infestation in pre-school children in the Eastern Cape (EC) and in northern KZN.[30] Helminthiasis ranged from 20% in children less than 1 year old in the EC to 46% in 5-year-olds in KZN. The prevalence of *Giardia* ranged from 9% in children less than 1 year old to 26% in children who were 4–5 years old. In 2004, results of a hospital-based survey in the EC suggested that 28–50% of epilepsy cases might be caused by tapeworm cysts in the brain.[26] Many of the epileptics are children.

If it becomes legally and physically possible to implement group-based deworming in South Africa, the aspects outlined in the following three sections will be of importance.

Safety of deworming

Health personnel, administrators in education, teachers and parents are inevitably concerned about safety and possible adverse effects of deworming. As specified previously, close to 200 000 doses of mebendazole have been dispensed as 500-mg single-dose tablets during the course of research projects in the south-western Cape.[12–14,20,24,32] Most of these treatments have been by teachers or lay persons. No reports of adverse effects have been received. While it is clear that children want to be treated, those who need to treat them are confused by incorrect information in the package-inserts.

Quality of deworming medicine

All batches of deworming medicine should be independently checked for quality. This has been done in operational research projects carried out by the MRC. On two occasions, South African generic mebendazole tablets did not match specifications for polymorph configuration. Pharmacological facilities are available locally for assessing the quality of mebendazole (and other anthelmintics) in terms of active ingredient quality and content, dissolution and tablet hardness.[57] These tests should be a routine procedure.

Sentinel surveys in relation to public and environmental health

It is possible that we are in a deteriorating situation with regard to infection by helminths and protozoal pathogens, similar to that reflected by ongoing cholera outbreaks. The scale of migration into urban and periurban environments has exceeded the capacity to provide services. Taking Khayelitsha as an example, the population density where people live in shacks ranges between 2250 and 33 786 per km^2 (mean 15 653 per km^2). Before the influx of so many people, most of the area was clean in terms of pollution by human faecal material, because nobody lived there.[12] Explosive migration into unserviced areas could cause the rate of infection, by intestinal parasites and enteric disease in general, to increase. Sentinel, school-based surveys at intervals of three to five years should be ongoing in order to monitor parasitic infections as appropriate to local conditions.[4–32] This can be done by using basic, inexpensive techniques and would be more cost-effective and manageable than larger-scale surveys. Sustained checking where epidemiological risks are high would gauge the overall threat of enteric diseases as well as assess the effectiveness of interventions.[58,59] It is important to note that microscopy of faecal samples is not reliable for the detection of enterobiasis[23] or taeniasis (*Taenia solium* is the source of cysticercosis[26]). When laboratory diagnostic facilities are not available, simple questionnaires can yield key information, such as the frequency of blood in urine or faeces as an indication of schistosomiasis,[31,60] or of big worms in faeces or vomit as confirmation of ascariasis. Successful school-based deworming can stimulate increased demand from non-target groups, which health centres should be ready to service.

Recommendations

1. There needs to be an effective partnership between health, education and research services, both nationally and in all provinces, in order to optimize delivery of school- and crêche-based deworming. Collaboration should

extend to the development and use of locally relevant health education, as well as improvement in all aspects of sanitation and hygiene.

2. Authorization is needed for non-medical and some paramedical personnel to carry out deworming treatments with S0 and S1 anthelmintics, as well as to obtain informed consent and participate in management and administration. In particular, teachers, parents, EHOs and community health workers should be legally entitled to deworm children in schools, crêches, orphanages and some other institutions.
3. Albendazole and praziquantel should be de-scheduled to S1 or S0 to enable unimpeded use for group-based deworming. For the same reason, ivermectin and levamisole should either be registered, or an exemption authorizing procurement and use should be issued. They could then be alternated with benzimidazoles to reduce the risk of development of resistance to mebendazole and albendazole. Nitazoxanide is now registered in nine South American countries as an anthelmintic and antiprotozoal medicine, and in the United States for the treatment of giardiasis and cryptosporidiosis. This product might become useful in South Africa.
4. Procurement and use of medicine from the cheapest source, including suppliers outside South Africa, needs to be permitted, with monitoring in South Africa of pharmacological quality as a requirement.

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