Unfulfilled potential: using diethylcarbamazine-fortified salt to eliminate lymphatic filariasis

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Abstract Fortifying salt with diethylcarbamazine (DEC) is a safe, low-cost and effective strategy to eliminate transmission of lymphatic filariasis. DEC-fortified salt has been used successfully in pilot projects in several countries and has been used operationally by China to eliminate lymphatic filariasis. The successful use of iodized salt to eliminate iodine-deficiency disorders is encouraging; similarly, fortified salt could be used as a vehicle to eliminate lymphatic filariasis. Despite the potential programmatic advantages of fortifying salt with DEC instead of undertaking mass administration of tablets, DEC-fortified salt remains an underutilized intervention. We discuss the reasons for this and suggest settings in which the use of DEC-fortified salt should be considered.

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Une traduction en français de ce résumé figure à la fin de l'article. Al final del artículo se facilita una traducción al español. الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

Introduction

Unbeknownst to many, a global effort is being undertaken to eliminate the parasitic disease colloquially known as elephantiasis. This little-known public health effort against lymphatic filariasis has achieved considerable momentum and successes, but is competing for scarce global funding. Approximately 80 million people in more than 75 countries harbour the transmission stages of *Wuchereria bancrofti* and *Brugia malayi*, the disease's causative agents. An additional 40 million people are affected by disfiguring damage to their limbs and genitalia, making the disease a leading cause of disability worldwide.[1,2] Interrupting transmission of the disease requires careful identification of endemic areas and the use of drugs designed to reduce microfilaraemia and break the transmission cycle. The mapping of areas endemic for *W. bancrofti* has been made easier with the use of a rapid antigen detection test.[3,4] The standard drug intervention has been simplified from a 12-day regimen, often directed at people with clinical disease, to mass drug administration for at-risk populations of a single annual dose of a two-drug regimen.[5] With the advent of these new diagnostic and therapeutic approaches as well as strategies to control morbidity, widespread interest has developed in eliminating these infections. As a result, the World Health Assembly called for the elimination of lymphatic filariasis to become a global public health goal.[5] Most endemic countries have now initiated or completed mapping, and more than 30 have established programmes that use albendazole and either ivermectin or diethylcarbamazine (DEC) for mass drug administration programmes.[6]

The single greatest barrier to expanding elimination programmes to all at-risk people is financing. Although mass drug administration programmes have been successful in reducing microfilaraemia and providing important collateral de-worming benefits, elimination programmes are competing for scarce public health dollars.[7–9] Additional barriers to implementing filariasis elimination programmes based on mass drug administration include the difficulty of developing an infrastructure capable of distributing drugs to the entire at-risk population, the need to achieve and maintain high coverage levels for 5 years or more, and diminishing compliance over subsequent cycles of mass drug administration because of adverse reactions associated with the parasite's death following treatment.[10,11] As discussed in greater detail below, salt fortified with DEC offers an alternative to mass drug administration and has the potential to overcome these obstacles; it could, in principle, eliminate filariasis faster and more cost-effectively than tablet-based programmes.[12–16]

Despite its theoretical advantages, DEC-fortified salt has not been embraced by the lymphatic filariasis community as a public health intervention. Ironically, two major public health successes have also not received the public attention they deserve and they have direct relevance to the use of DEC-fortified salt. First, China, the country with the largest number of cases and largest population at risk, has eliminated transmission of the disease owing to, at least partly, the use of DEC-fortified salt.[17,18] Second, the salt industry has been mobilized on a country-by-country basis to increase the household use of iodized salt from low levels worldwide to more than

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70% globally within the past 15 years; this has resulted in the likely elimination of cretinism, the most severe form of iodine deficiency, as well as a dramatic reduction in less severe iodine-deficiency disorders, and it has likely improved the IQ of millions of people.[19–21] These two successes highlight the importance of considering the contribution that salt containing DEC and iodine could make to the global effort to prevent lymphatic filariasis.

DEC salt: the other intervention

In 1967, at a time when lymphatic filariasis was being addressed primarily as a clinical problem by case identification and its standard treatment was a 12-day regimen, initial studies were done on using DEC-fortified salt to reduce microfilaraemia.[22] These studies showed that DEC did not alter the colour or taste of salt, that it was stable in cooking and that it retained its efficacy in reducing microfilaraemia even when used in this fashion. The scientific efficacy of DEC-fortified salt is well established; pilot studies in Brazil,[22] Haiti,[13] India[23,24] and the United Republic of Tanzania[12,25,26] have all shown that DEC-fortified salt reduces microfilaraemia. The studies in the United Republic of Tanzania that compared different DEC interventions suggested that DEC-fortified salt provided a longer-lasting reduction in microfilaraemia than DEC tablets.[14,25]

Regional programmes in China[17,18,27,28] and India[29,30] have demonstrated success with DEC salt interventions at the programmatic level. DEC-fortified salt was used extensively in China, both alone and in combination with mass drug administration. China previously had the largest number of people with lymphatic filariasis, and hundreds of millions were living in endemic areas. Each province in China used different combinations of interventions, but more than 194 000 000 people used DEC-fortified salt; in some provinces it was the principal intervention.[17] In 1994, all provinces in China had reached the criteria for basic elimination of filariasis, and according to national experts DEC-fortified salt played a critical part.[17]

One programmatic advantage of using DEC-fortified salt is that it causes few or no adverse reactions when compared with DEC tablets. During mass drug administration the proportion of people who experience mild adverse reactions may approximate the prevalence of microfilaraemia in the community. Although these reactions typically are not serious, adverse events do contribute to noncompliance.[10,11] Although the impact of noncompliance on efforts to interrupt transmission is not known, there is concern that mass drug administration will not be successful if coverage declines because of noncompliance. Adverse reactions following the use of DEC-fortified salt are mild or absent, and thus they should not exacerbate issues of noncompliance.[13,15,17,31] It is important to point out that the use of DEC is contraindicated in people with onchocerciasis because of fears of ocular damage associated with death of microfilariae in the eye.[32,33] Although one pilot study of the use of DEC-fortified salt by patients with onchocerciasis has been done, additional clinical research is needed to determine whether lower doses of DEC can be delivered in salt without provoking inflammatory pathology.[34]

The length of time required to interrupt transmission of lymphatic filariasis, whether through mass drug administration or using DEC-fortified salt, is not known, so it can be estimated only from mathematical models.[35,36] Both interventions depend on effective social mobilization to maximize coverage. Assuming equal coverage, the duration of a DEC-fortified salt programme should not need to be as long as the duration of a mass drug administration programme, both because of its greater effectiveness and because of its likely prophylactic benefit against infective larvae. This antilarval effect is the basis for periodically administering DEC tablets for prophylaxis against infections with *Loa loa* as well as preventing infections with *Dirofilaria* in veterinary medicine.[37,38] DEC-fortified salt also may achieve higher effective coverage through the consumption of foods prepared with DEC-fortified salt outside the home by people not using fortified salt in their own households.

Despite its real and theoretical advantages and the success in China, DEC-fortified salt remains an underutilized intervention. This likely reflects a combination of technical and behavioural barriers. A significant technical obstacle to the use of DEC-fortified salt is related to the recommendation that DEC not be used in areas where loiasis or onchocerciasis is endemic because of the potential for adverse events. Other barriers play a part: lack of experience in managing a commodity like salt may be a disincentive for initiating a programme to fortify salt with DEC. Many public health managers have no experience working with manufacturers and distributors largely from the private sector, and this partnership calls for expanding public health skills. The long history of tablet-based treatment for microfilaria carriers, the familiarity of annual mass treatment campaigns and the added benefit of donated albendazole for de-worming may lead programme managers to overlook the DEC-fortified-salt option.

Linking to salt iodization

In 1990, the World Summit for Children included the elimination of iodine-deficiency disorders as a critical goal for the decade. Iodine deficiency, having been for the most part eliminated from the developed world, remained highly prevalent in poorer countries and thus remained the leading cause of preventable mental impairment worldwide. Over the subsequent decade, national salt iodization programmes were established in virtually all endemic countries, resulting in more than 70% of households using iodized salt and a dramatic reduction in iodine deficiency.[19–21] This public health success was the result of working in partnership with the salt industry. The partnership used advocacy, provided assistance with capital costs for the purchase of iodization equipment, established laboratories at production facilities, subsidized the purchase of potassium iodate, and supported educational and promotional efforts at the national level.

The dramatic success of salt iodization globally has increased the potential for adding DEC to salt, thereby enabling a link to be made between programmes for eliminating filariasis and those for eliminating iodine deficiency. From a technical perspective, adding DEC to an existing salt fortification process is as straightforward as adding iodine to salt. DEC can be added in the same fashion as iodine regardless of whether iodine is added to salt as part of a dry mix or sprayed on as a liquid. Increased attention to quality control is needed in both instances to verify that the iodine and DEC levels are in the appropriate therapeutic range (0.1–0.6%

by weight for DEC), but the experience with quality control gained by iodization programmes has shown that this can be done. From the programmatic perspective, a pilot study conducted in a community with both lymphatic filariasis and iodine deficiency showed that 12 months of use of salt fortified with DEC and iodine led to dramatic declines in both microfilaraemia and iodine deficiency.[13]

The Guyana experience

Lymphatic filariasis is endemic in Guyana's coastal belt, where 80% of the population lives. Limited availability of health staff led the Ministry of Health to select DEC-fortified salt rather than tablet-based mass drug administration as the basis of their elimination strategy. The programme in Guyana is the first of its kind: a national programme to eliminate lymphatic filariasis based on the introduction of DEC-fortified salt into a competitive market. Social mobilization activities and the launch of the product in July 2003 were extremely successful, based on assessments of the knowledge of DEC-fortified salt and the rapid initial sales of the product. Three key factors that had a role in the early success of the programme stand out as important lessons to be shared with other countries considering the use of DEC-fortified salt.

- A permissive regulatory environment is necessary so that DEC-fortified salt can be made available as a food product and not as a pharmaceutical.
- Strong partnerships with salt producers and importers are required so that normal marketing channels can be used to introduce and sell DEC-fortified salt.
- Social marketing is critical to build consumer demand for DEC-fortified salt.

After early successes with the marketing of DEC-fortified salt, consumer confidence was impacted by problems associated with discoloured salt, followed by disruptions in the overall salt supply. Although technical problems appear to have been resolved by increasing quality control, consumer demand for DEC-fortified salt has not reached previous levels. Several factors may be responsible for lower coverage, including the limited availability of DEC-fortified salt. With periodic interruption of household salt supplies and only a single producer manufacturing the fortified salt, it is difficult for distribution networks created by a single importer to reach all retail outlets. In addition, DEC-fortified salt competes with unfortified salt brought in by other importers. This is an important lesson for other countries considering the use of DEC-fortified salt. Unfortified salt is often unpackaged and may threaten the lymphatic filariasis elimination programme because it costs less. To support both iodization and lymphatic filariasis elimination programmes, either more restrictive regulatory controls are needed, including enforced consumer packaging, or governments need to develop active partnerships with importers and salt producers to increase supplies of and consumer demand for DEC-fortified salt.

Other opportunities

The initial consumer demand created in Guyana for DEC-fortified salt makes the case that the strategy for salt fortification should be considered more widely than it has been. Lessons learned from Guyana can be applied to other countries to increase programme success. Settings where salt iodization programmes have achieved high coverage and where iodization is mandated offer the best opportunities, and in such settings, integrating fortification with DEC into existing salt iodization programmes may offer a simple, rapid approach to eliminating lymphatic filariasis. In the context of a functioning iodization programme, existing salt distribution networks can be exploited and the costs for the intervention are largely driven by the cost of the DEC, approximately US$ 0.05–0.10 per person per year. Such costs compare favourably with annual costs for mass drug administration in many countries[39,40] and fortification with DEC has been noted to be a cost-effective intervention by the Disease Control Priorities Project (a joint project of the Fogarty International Center of the US National Institutes of Health, WHO and the World Bank).[41]

In countries with efficient vector transmission, such as areas of the Pacific where *Aedes polynesiensis* is the vector, DEC-fortified salt could have a critical role in eliminating transmission by maintaining a low level of drug pressure to provide a prophylactic benefit as well as a therapeutic benefit. DEC-fortified salt also represents an attractive programmatic option where traditional approaches to tablet distribution are likely to be problematic because of cost or persistently low coverage, or in rapidly expanding urban areas where health infrastructure and social services have not kept pace with population growth. In sub-Saharan Africa, where *Onchocerca volvulus* is found, it will also be necessary to determine whether DEC-fortified salt alone or following treatment with ivermectin can be used safely in people with low levels of microfilariae in their skin. If so, this also would open the door to the use of DEC-fortified salt, especially in urban areas or where onchocerciasis control programmes have been implemented and have led to low levels of *O. volvulus* infection.[42] In the latter context, DEC-fortified salt could play a significant role in maintaining gains achieved by mass drug administration and could alleviate concerns that have arisen about the potential for development of resistance to ivermectin.[43]

Conclusions

The iodization of salt stands out as a tremendous public health success, a model of a safe and effective programme. Adding DEC to salt that is being iodized is straightforward: there is no incompatibility between the two additives and the fortification process is identical. Salt is used in relatively consistent amounts in all countries, and all countries have an established salt production or importation and distribution system. Thus, with government commitment, establishing a programme to fortify salt with DEC and distribute it to eliminate lymphatic filariasis does not need to be complicated. What is needed at the country level is review of how salt is manufactured or imported and distributed (a salt situation analysis) and the salt iodization programme as well as development of a strategy to prepare the salt industry to produce DEC-fortified salt.[44] Establishing a DEC-fortified salt programme is likely to greatly enhance the possibility of sustaining reductions in microfilaraemia below the point where transmission is possible, and salt fortification should not be overlooked as an important approach for eliminating transmission of lymphatic filariasis. The success in China with DEC-fortified salt highlights its contribution, and the success with salt iodization provides the opportunity. ■

Competing interests: None declared.

Résumé

L'utilisation de sel de cuisine enrichi en diéthylcarbamazine pour éliminer la filariose lymphatique: un potentiel partiellement inutilisé

L'enrichissement du sel de cuisine avec de la diéthylcarbamazine (DEC) constitue une stratégie sans risque, économique et efficace pour éliminer la transmission de la filariose lymphatique. Le sel enrichi en DEC a été employé avec succès dans des projets pilotes menés par plusieurs pays et de manière opérationnelle en Chine pour éliminer la filariose lymphatique. Malgré les avantages que pourrait avoir, dans le cadre des programmes de lutte contre la filariose, l'utilisation de sel enrichi en DEC au lieu d'une administration massive de comprimés de ce produit, cette possibilité reste sous-exploitée. Nous avons examiné les raisons de cette situation et proposé des lieux où l'on pourrait envisager d'utiliser du sel ainsi enrichi.

Resumen

Una posibilidad desaprovechada: el uso de sal enriquecida con dietilcarbamazina para eliminar la filariasis linfática

El enriquecimiento de la sal con dietilcarbamazina (DEC) es una estrategia segura, de bajo costo y eficaz para eliminar la transmisión de la filariasis linfática. La sal enriquecida con DEC se ha empleado con éxito en proyectos piloto emprendidos en varios países y ha sido utilizada operacionalmente por China para eliminar esa enfermedad. El éxito conseguido con la sal yodada para eliminar los trastornos por carencia de yodo es alentador; de forma parecida, la sal enriquecida podría utilizarse como vehículo para eliminar la filariasis linfática. Pese a las ventajas programáticas potenciales del enriquecimiento de la sal con DEC, por oposición a la administración masiva de comprimidos, esa alternativa sigue siendo una intervención infrautilizada. Analizamos las razones de ello, y señalamos en qué circunstancias se debería considerar la posibilidad de emplear sal enriquecida con DEC.

ملخص

إمكانية لم تتحقق: استخدام الملح المقوَّى بدي إيثيل كاربامازين للتخلُّص من داء الفيلاريات اللمفي

تعد تقوية الملح بدي إيثيل كاربامازين استـراتيجية مأمونة ورخيصة وفعّالة للتخلُّص من سراية داء الفيلاريات اللمفي. وقد استُخْدِم الملح المقوَّى بدي إيثيل كاربامازين في مشاريع ارتيادية في العديد من البلدان، كما استُخْدِم بنجاح ميداني في الصين للتخلص من داء الفيلاريات اللمفي؛ وقد كان النجاح في استخدام الملح الـمُيَوْدَن للتخلُّص من عوز اليود مشجعاً؛ إذ يمكن استخدام الملح المقوَّى كأداة ناقلة لدي إيثيل كاربامازين للتخلُّص من داء الفيلاريات اللمفي بدلاً من تنفيذ حملات جموعية لإعطاء الأقراص، إلا أن الملح المقوَّى بدي إيثيل كاربامازين لايزال من التدخلات القليلة الاستخدام. وقد ناقشنا هذه الأسباب واقترحنا المواقع التي يمكن تطبيق هذه الاستراتيجية فيها.

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