Salt fortified with diethylcarbamazine (DEC) as an effective intervention for lymphatic filariasis, with lessons learned from salt iodization programmes

R. HOUSTON*

9455 Big Gulch, Bozeman, Montana, 59715, USA

SUMMARY

DEC-fortified salt has been used successfully as a principal public health tool to eliminate lymphatic filariasis (LF) in China and, less extensively, in several other countries. Studies from 1967 to the present conducted in Brazil, Japan, Tanzania, India, China, and Taiwan involving administration of DEC salt for 18 days to 1 year, have shown this intervention to be effective for both bancroftian and brugian filariasis, as measured by reductions in both microfilarial density and positivity, and in some studies through reduction in mosquito positivity rates as well. Furthermore, studies suggest specific advantages from using DEC salt, including lack of side effects, particularly for bancroftian filariasis, and ability to reduce prevalence below 1% when used in conjunction with standard regimens of DEC tablets. However, use of DEC salt as a control tool suffers from a concern that health authorities might find it difficult to manage a programme involving a commodity such as salt. In the past decade, the very successful global efforts to eliminate iodine deficiency through universal salt iodization have demonstrated that partnership with the salt industry can be both successful and effective as a public health tool. Use of DEC salt can be most successfully implemented in areas in which (a) there is adequate governmental support for its use and for elimination of filariasis, (b) filariasis-endemic areas are clearly defined, (c) political leaders, health officials and the salt industry agree that DEC salt is an appropriate intervention, (d) the salt industry is well-organized and has known distribution patterns, (e) a successful national salt iodization effort exists, (f) a monitoring system exists that ensures adequacy of salt iodine content during production and that can also measure household coverage, and (g) measurement of impact on transmission of LF with the new antigen or filarial DNA detection methods can be established. There are advantages and disadvantages of using DEC-fortified salt compared with other interventions for LF elimination programmes, but rather than being considered as a 'competing' intervention, DEC salt should be seen as an additional option. Indeed, it is likely that many countries will derive maximal benefit from the synergistic effects of combining different intervention strategies in their national programmes to eliminate lymphatic filariasis.

Key words: DEC salt, diethylcarbamazine, lymphatic filariasis, bancrofian filariasis, brugian filariasis, *Wuchereria bancrofti*, *Brugia malayi*, tropical disease control, microfilaraemias, iodization of salt, iodine deficiency disorders.

INTRODUCTION

With the recent successes of polio and guinea worm control programmes and their rapid progress toward eradication, there is renewed interest among governments and donor agencies to address other diseases that might be eliminated, particularly lymphatic filariasis (LF). In establishing a national plan to eliminate lymphatic filariasis, managers must decide what intervention or combination of interventions to use. There is a growing literature on a variety of interventions focused primarily on mass drug administration to achieve LF elimination (Ottesen *et al*. 1997) and also a wealth of information already available on other mass intervention campaigns, e.g. those of polio eradication or, more recently, vitamin A supplementation (WHO, 1998). However, much less has been written about another extremely effective intervention to eliminate lymphatic filariasis; namely, salt fortification with diethylcarbamazine (DEC) (Gelband, 1994).

DEC-fortified salt has been used successfully as a principal public health tool to eliminate LF in China (Lui *et al*. 1992) and, less extensively, in several other countries, as well. However, this intervention suffers from a concern that health authorities might find it difficult to manage a programme involving a commodity such as salt. In the past decade, the very successful global efforts to eliminate iodine deficiency through universal salt iodization have demonstrated that partnership with the salt industry can be both successful and effective as a public health tool (Mannar & Dunn, 1995). Therefore, while there are advantages and disadvantages of using DEC-fortified salt compared to other interventions for LF elimination programmes, rather than being considered as a 'competing' intervention, DEC salt should be seen as an additional option. Indeed, it is likely that many countries will derive maximal benefit from the synergistic effects of combining different intervention strategies.

* Phone/Fax: 1-406-582-7959.
E-mail: houstonr@mcn.net

Parasitology (2000), **121**, S161–S173. Printed in the United Kingdom
https://doi.org/10.1017/S0031182000007150 Published online by Cambridge University Press

The problem of lymphatic filariasis and the tools for its solution

The 50th World Health Assembly passed a resolution in 1997 which identified elimination of lymphatic filariasis as a public health priority. This resolution was passed because of the increasing recognition of the magnitude and severity of the problem of LF and because new diagnostic and treatment regimens make elimination possible. The World Health Organization has estimated that 1·1 billion people live in areas where they are at risk of contracting lymphatic filariasis, that 120 million people are infected, and that 76 million already have damage to their lymphatic and renal systems (Ottesen *et al*. 1997). The disease is likely present in at least 80 countries, 38 of which are in Africa, but with the largest estimated number of infected individuals in South-East Asia. Within a country, the disease tends to be distributed in endemic 'pockets' with higher prevalences in some communities or community clusters, and very low prevalence in other areas (WHO, 1997). The World Health Report in 1995 ranked lymphatic filariasis as the second leading cause of permanent disability worldwide (WHO, 1995).

With respect to its transmission, lymphatic filariasis has a number of particularly important and distinctive features: (1) The disease persists in a population because the adult worms in infected humans produce microfilariae which are transmitted to other individuals in the population by a variety of mosquito species, including *Culex* spp., *Mansonia* spp., *Anopheles* spp. and *Aedes* spp. (2) Humans are the only reservoir of infection for *Wuchereria bancrofti*, the most common LF parasite that accounts for 90% of human infections, and there is only a small non-human reservoir for *Brugia malayi* parasite species. (3) Reduction in both the prevalence and density of microfilariae in the blood reduces transmission. (4) Several drug regimens as well as salt fortified with DEC dramatically reduce both prevalence and density of blood microfilariae, often within one month of treatment, and they have an effect that may last several years. Single-dose treatment with a dual drug regimen is as effective as longer treatment regimens. (5) There are several new diagnostic techniques that now make assessment of population infection rates very much easier. For bancroftian filariasis, it is now possible to detect the adult worm antigen (circulating filarial antigen or CFA) on finger-prick samples taken at any time of day. Levels of this antigen decrease to zero in successfully treated individuals when all adult worms have been killed. For both bancroftian and brugian filariasis, there are now promising assays for the parasite DNA which can detect very low concentrations of microfilariae in humans or in developing larvae in mosquitoes, thereby accurately detecting current infections. These new tools are useful in identifying infected populations and in monitoring progress towards elimination. (6) New clinical treatment regimens have been developed that are effective in reducing the disability caused by the disease, providing not only hope for the affected individual, but also creating advocates for the transmission-interruption preventive efforts.

Because of all these considerations WHO currently recommends the development of a national strategy to eliminate lymphatic filariasis that incorporates: (a) rapid epidemiologic assessment to identify the populations within a country where LF elimination efforts should be focused; (b) an intervention programme that uses a combination of albendazole and either ivermectin or DEC depending on the country situation; (c) annual mass drug distribution for all those in endemic communities for 4–6 years; or substitution of DEC-fortified salt for regular table salt for all those in endemic communities for 1 single year; (d) community-focused intervention activities including patient treatment and management programmes; and (e) close monitoring of programme activities, including coverage and impact. In parts of Africa, the co-existence of lymphatic filariasis with the other filarial infections *Onchocerca volvulus* or *Loa loa* makes use of DEC dangerous because of the potential for severe reactions to the rapid killing of the microfilariae of these species that is induced by DEC; thus in those areas the combination of albendazole and ivermectin is recommended.

Strategic options

Table 1 shows the current mass campaign drug regimens recommended by WHO and the regimen for DEC-fortified salt. Several important issues must be considered in determining the best intervention or combination of interventions to use. First, the most appropriate drug regimen will depend on whether onchocerciasis or loiasis exists in the country – their presence currently precludes the use of DEC in either mass campaign or in fortified salt. Second, there still may be adverse reactions associated with single-dose mass drug distribution campaigns, since rapid killing of microfilariae may cause transient systemic symptoms (particularly headache and fever), and since killing the adult worms can cause transient tenderness and swelling where the adult worm 'nests' are located. Most DEC-fortified salt programmes, in contrast, have reported few or no side effects, though these may be somewhat more with brugian filariasis than with bancroftian filariasis (Shenoy, Varghese & Kuttikkal, 1998). Third, countries will have had different degrees of success with other community-wide public health campaigns and with salt fortification (particularly salt iodization) efforts. Good success

Table 1. WHO community treatment regimens for eliminating transmission of lymphatic filariasis*

Drug regimen	Dose	Duration
For areas without overlapping distribution of onchocerciasis or loiasis		
Albendazole plus	400 mg	Once annually, 'single dose'
DEC	6 mg/kg body weight	coadministered for 4–6 years
Albendazole plus	400 mg	Once annually, 'single dose'
Ivermectin	200 μg/kg body weight	coadministered for 4–6 years
DEC Salt	0·2–0·4 % w/w	Substituted for table/cooking salt for 6–12 months
For areas with overlapping distribution of onchocerciasis or loiasis		
Albendazole plus	400 mg	Once annually, 'single dose'
Ivermectin	200 μg/kg body weight	coadministered for 4–6 years
Ivermectin	400 μg/kg body weight	Once annually, single dose for 4–6 years

* Adapted from Ottesen *et al*. (1997)

with polio, vitamin A or de-worming mass campaigns may be a good predictor for success with a filariasis mass treatment campaign since the capacity to mount such a campaign is already proven. In addition, such successes may make initiation of a mass drug distribution for filariasis easier through use of an infrastructure already developed including the community support mechanisms and other programmatic components of the earlier campaigns. In the absence of such experience, particularly if there has already been a strong national salt iodization programme, DEC-fortified salt may be easier to implement.

Our understanding of lymphatic filariasis and the means to define its prevalence in populations, to intervene with simplified control methods, and to manage clinical cases have improved dramatically in the past decade. With these new tools, countries will be better able to implement control programmes leading to LF elimination, and the experience from research efforts and smaller pilot programmes can be helpful in scaling up to establish national programmes. DEC-fortified salt remains an effective intervention option. Understanding both the successful partnership with the salt industry for salt iodization, and the programmatic issues required for launching a mass distribution campaign will be critical for countries as they define their national strategies.

HISTORY OF DEC-FORTIFIED SALT USAGE IN LYMPHATIC FILARIASIS

Diethylcarbamazine was studied as a filaricidal agent as early as 1947 (Hawking, Sewell & Thurston, 1950). DEC rapidly became the mainstay of filariasis treatment and over the subsequent decades millions of treatment doses were dispensed. Following demonstration of efficacy against lymphatic filariasis, but with some concerns about side effects for mass treatment as part of control efforts, the concept of fortifying salt with DEC was pioneered by Hawking in Brazil in 1967. This early study demonstrated that DEC was stable in a food product, that its consumption reduced microfilarial prevalence and density, and that side effects from such a regimen were minimal (Hawking & Marquez, 1967). This landmark study established DEC-fortified salt as an additional intervention for filariasis elimination efforts.

Several important studies followed Hawking's work. Soup and a flavoured drink were fortified with DEC in Japan; dramatic reductions in microfilarial positivity rates were demonstrated within a few months of treatment (Kanda *et al*. 1967). Community-based studies in Tanzania in 1969 again demonstrated reduction in mean microfilarial densities by 90 % following 6 months' administration of DEC-fortified salt (Davis & Bailey, 1969). Studies in India, with a shorter period of administration of DEC salt, demonstrated similar results, with a suggestion that the response is somewhat dose dependent (Sen *et al*. 1974; Rao *et al*. 1976). In China, in 1976, much more extensive trials were completed in Shantung province. In these, DEC salt was given for 6 months to 32 villages with over 35,000 people. While these villages had had mass screening and treatment in the past, the microfilaria positivity rate had remained at 4·6 %. As with the studies in India and Tanzania, following initiation of DEC-salt microfilarial densities declined and the positivity rate fell to 0·23 % within 6 months (Dept. Filariasis, 1976). All of these studies involved intervention for *Wuchereria bancrofti* filariasis. None of the studies reported any significant side effects from the fortified salt intervention.

In 1980, further studies in China were carried out in several provinces where *Brugia malayi* was endemic. Although results were similar to the

https://doi.org/10.1017/S0031182000007150 Published online by Cambridge University Press

Table 2. Advantages and disadvantages of different treatment regimens for lymphatic filariasis

DEC salt	Mass 2-drug treatment campaign (DEC + Albendazole)
Simple to add to existing salt iodization infrastructure	May use infrastructure developed for other mass intervention campaign
May require review of food law to permit addition of pharmaceutical to food product	May require political advocacy for acceptance of repeated annual event
Requires initial staff effort to work with salt producers, followed by continuous effort for monitoring	Requires significant staff effort to prepare for and launch campaign, for shorter period annually
Coverage estimated by household salt use and simple salt test	Coverage estimated by household tablet receipt or tablet consumption
Minimal side effects expected	Side effects likely, especially in first rounds of treatment
Once DEC salt is accepted, coverage is likely to remain stable	Side effects or 'community fatigue' may reduce coverage for subsequent rounds
Gradual but persistent reduction of microfilaria density and prevalence; however, effect on adult worm unclear	Rapid and persistent reduction of microfilarial density and prevalence; kills proportion of adult worms
Single drug regimen	Dual drug regimen is more effective
Minimal effects on intestinal parasite infections	Dual regimen with albendazole reduces *Ascaris*, hookworm, *Trichuris* and thereby improves iron and nutritional status, particularly in women and children
IEC efforts needed to ensure acceptability by community, mostly initially	IEC efforts needed to promote campaign and ensure adequate coverage, for each round
Estimated programme costs are \$0·80/person/year (data from India), for 6–12 months of intervention	Estimated programme costs \$0·05–0·15/person/year (WHO, 1997) or US \$1·00/person/year (Ferrell *et al*. 2000) for 4–6 years

findings from the studies in Shantung, the final reduction in microfilarial positivity was not so complete. Also, there were some reported side effects from the DEC salt intervention, particularly in individuals with high brugian microfilarial densities (Zhong & Zheng, 1980). This result suggested that brugian filariasis might respond somewhat differently from bancroftian filariasis, with greater initial sensitivity reflected in greater side effects, but with a lower overall therapeutic response to the low-dose salt regimen.

The early studies with DEC were tightly controlled, with close monitoring of a number of indicators of infection rates and transmission. In China in particular, the approach for elimination was initially to identify cases through mass screening, and then to treat them. Subsequently, however, the strategies shifted toward identification not of individuals, but of infected communities, and mass treatment for the entire population. In the early 1990s, several follow-up studies in the Quemoy Islands, in Fujian and Shandong provinces in China and in Tanzania focused on the longer term results from DEC-fortified salt. In the Quemoy Islands' studies, the entire population was treated with DEC-fortified salt for 6 months in 1974. Follow-up surveys up to 1982 demonstrated a reduction in microfilarial positivity to zero, with the infection considered to have been eradicated from the island (Fan, 1990*a*). In a similar report, from Kinmen (Quemoy) Proper, initial mass distribution of DEC reduced microfilaria positivity substantially but did not accomplish complete elimination, an outcome attributed to a relatively high rate of initial side effects that affected compliance with subsequent distributions. DEC salt was subsequently used by the entire population for 6 months, and follow-up surveys demonstrated complete elimination (Fan, 1990*b*).

The successful elimination of filariasis from the Quemoy Islands was attributed in part to treatment of an entire isolated island population, thereby reducing the risk of re-infection from infected mosquitoes from adjacent communities in which the disease persists. Several long-term studies have demonstrated that the initial reduction in microfilarial positivity rates may not be preserved after 4 or more years, likely because of persistence of some adult worms or the inability of these studies to cover a large enough geographic area to prevent re-infection. In one study in India, DEC salt was provided to half the households within a village with significant reductions in microfilarial densities and prevalence in the treated group. These gains were, however, lost after 8 years and the recommendation was made to cover the entire endemic population (Krishnarao, Raminder & Ghosh, 1991). Subsequent

https://doi.org/10.1017/S0031182000007150 Published online by Cambridge University Press

Table 3. Summary of studies on DEC-fortified salt

Study	Intervention	Results	Side effects
Brazil (Hawking & Marquez, 1967) ($n = 2300$)	DEC salt, 0·2–0·4 % w/w (a) for 18 days (13·5 mg/kg total) and (b) for 40 days (186 mg/kg total)	(a) mf density reduced from 50 to 13·6 mf/40 mm^3 blood after 45 weeks. $n = 7$ mf positive patients (72·8 % reduction). (b) mf density reduced from 24 to 0·3 mf/40 mm^3 blood after 45 weeks. $n = 15$ mf positive patients (98·7 % reduction).	None
Japan (Kanda *et al.* 1967) ($n = 67$)	DEC in orangeade, 2 mg/kg body weight for 3 days, then 6 mg/kg for 11 days (72 mg/kg total)	mf density reduced from 19 to 0 mf/30 mm^3 blood (except 1 person with 1 mf seen) after 5 months (99 % reduction).	None
Tanzania (Davis & Bailey, 1969) ($n = 672$)	DEC salt, 0·1 % w/w for 6 months (42 mg/kg total)	mf density reduced from 44·3 to 4·6 mf/30 mm^3 blood after 6 months. $n = 64$ mf positive patients (89·6 % reduction).	None
India (Sen *et al.* 1974) ($n = 340$)	DEC salt, 0·26 % w/w for 11 weeks (83 mg/kg total)	mf density reduced from 48 to 8·25 mf/20 mm^3 blood after 11 weeks. $n = 28$ mf positive patients (82·8 % reduction).	None
India (Rao *et al.* 1976) ($n = 1227$)	DEC salt, 0·1 % w/w over 45 weeks (100 mg/kg total)	mf density reduced from 47·5 to 2·5 mf/20 mm^3 blood after 2 years (95 % reduction); and from 47·5 to 5·8 mf/20 mm^3 blood after 5 years (87·8 % reduction). $n = 323$ mf positive patients.	None mentioned
China (Dept. Filariasis, 1976) ($n = 5626$)	DEC salt, 0·3 % w/w over 6 months (150 mg/kg total)	mf density reduced from 51 to 4·7 mf/120 mm^3 blood after 6 months (90·1 % reduction); and from 51 to 2·7 mf/120 mm^3 blood after 1 year (94·7 % reduction). $n = 281$ mf positive patients.	None
Taiwan (Fan, 1990*a*) ($n = 7125$)	DEC salt, 0·33 % w/w for 6 months (126 mg/kg total)	mf density reduced from 14·4 to 1·8 mf/20 mm^3 blood after 6 months (87·5 % reduction). $n = 459$ mf positive patients.	None
Taiwan (Fan, 1990*b*) ($n = 12912$)	(a) DEC mass treatment, 5 g total given over 10–12 days, annually for 3 years (83 mg/kg total) (b) DEC salt, 0·33 % w/w for 6 months (126 mg/kg total)	(a) mf density reduced from 14·6 to 5·3 mf/20 mm^3 blood after 3 years (63·7 % reduction). $n = 3853$ mf positive patients. (b) mf density reduced from 5·3 to 2·5 mf/20 mm^3 blood after 4 months (52·8 % reduction). $n = 55$ mf positive patients, and from 5·3 to 0 mf/20 mm^3 blood after 6 months (100 % reduction).	Moderate None
India (Krishnarao *et al.* 1991) ($n = 203$)	DEC salt, 0·2 % w/w for 6 months (123 mg/kg total)	mf density reduced from 22·7 to 5·2 mf/20 mm^3 blood after 6 months (77·1 % reduction) $n = 48$ mf positive patients, and from 22·7 to 18·1 mf/20 mm^3 blood after 8 years (20·2 % reduction).	–
India (Panicker *et al.* 1997) ($n = 18$)	DEC salt, 0·2 % w/w for 30 weeks (87·5 mg/kg total)	mf density reduced from 20·6 to 0 mf/20 mm^3 blood after 30 weeks (100 % reduction)	Moderate (brugian)
India (Shenoy *et al.* 1998) ($n = 20$)	DEC salt, 0·2 % w/w for 1 year (130 mg/kg total)	mf density reduced from 894 to 192 mf/ml blood after 1 year (78·5 % reduction). $n = 20$ mf positive patients.	Moderate (brugian)
Tanzania (Meyrowitsch & Simonsen, 1998) ($n = 68$)	DEC salt, 0·33 % w/w for 1 year (200 mg/kg total)	mf density reduced from 1288 to 9 mf/ml blood after 4 years (99·3 % reduction). $n = 68$ mf positive patients.	None

work in Shandong and Fujian provinces in China, with repeated monitoring, also showed encouraging results with persistently low positivity rates when the entire populations had been treated even 10 years previously (Zhong & Zhen, 1991; Lui *et al*. 1992). A summary overview of the Chinese programme, which used various combinations of mass examination and treatment and DEC salt, indicates clearly that DEC salt was critical in achieving elimination below 1 % microfilarial prevalence for the country as a whole and subsequent elimination of the infection entirely (De-Jian, 1994).

A follow-up study carried out after the successful eradication of filariasis from the Quemoy Islands reviewed the clinical aspects of filariasis and showed that most acute clinical symptoms (such as lymphangitis and lymph node enlargement) had either disappeared or improved in the 16–19 years following eradication. Chronic symptoms including elephantiasis of the lower extremities did not improve, however (Fan, Peng & Chen, 1995), and this finding emphasizes again the importance of concurrent clinical management programmes using the newer treatment regimens for elephantiasis, as part of the overall LF elimination effort.

A recent experimental study in Tanzania compared four different DEC interventions over a 4-year period, reviewing both individual outcomes and community outcomes. This study again confirmed that DEC salt is equally as effective as multiple day treatment, as semi-annual single-dose and as monthly low-dose regimens (Meyrowitsch & Simonsen, 1998). These studies raised interesting questions about reinfection following intervention, showing clearly that individuals who have been microfilaremic are more likely to become microfilaraemic again. This likely suggests that in some individuals the treatment has not been adequate to kill the adult worms, or less likely, that some individuals are immunologically more susceptible to repeat infections.

In summary, in studies from 1967 to the present, DEC-fortified salt has been shown to be an effective intervention for both bancroftian and brugian filariasis. This effectiveness has been demonstrated at the individual level and at the community level through reductions in microfilarial density, reduction in microfilarial positivity, and in some studies through reduction in mosquito infectivity rates. Furthermore, the studies suggest some specific advantages from using DEC salt: (1) Most studies report that there were no side effects during DEC salt administration, particularly for bancroftian filariasis. Transient side effects were reported in several studies for brugian filariasis, although all studies reported that these did not affect compliance. (2) Several studies, particularly in China and Taiwan, report that mass distribution of DEC tablets in standard regimens was successful in reducing prevalence to a certain point, but that DEC salt appears to have been instrumental in completing that reduction to levels below 1 %. (3) In most locations reporting success in elimination (several provinces in China, Quemoy Islands in Taiwan) a combination of interventions was used, with mass distribution of DEC tablets followed by DEC salt.

Table 2 outlines some of the advantages and disadvantages of DEC salt compared to a mass, DEC single-dose, 2-drug treatment campaign that includes DEC. Table 3 summarizes a number of representative studies showing reductions in microfilarial prevalence and in microfilarial densities and the time periods involved.

Even such positive results from studies on DEC salt have not, however, resulted in widespread adoption of this intervention for filariasis programmes. Part of the reason for this may be the lack of experience within the public health community in managing an intervention involving a food commodity. Except for those in the field of nutrition, most clinicians and other health professionals have not dealt extensively with industry other than the pharmaceutical industry, and there are many perceived difficulties in launching an intervention requiring fortification of salt. Within the past decade there has been extraordinary success with 'universal salt iodization' that has depended importantly on close collaboration between health ministries and the salt industry. This experience has greatly improved the potential for successful use of DEC salt as an additional intervention for filariasis.

IODINE DEFICIENCY AND THE USE OF SALT FORTIFICATION TO OVERCOME IT

Although iodine was identified in the early 1800s, it was not until a century later that the element was determined to play a critical role in human growth and development. Enlargement of the thyroid gland or goitre as an expression of iodine deficiency, has been noted in art work before the Renaissance, but it was not until the more recent discovery that even sub-clinical deficiency results in impaired mental development, that iodine deficiency was recognized as a significant public health problem. Iodine deficiency is now accepted as the leading cause of preventable mental impairment worldwide, with over a billion people at risk (see discussion of Iodine Deficiency Disorders, in Global Malnutrition, this supplement).

Though some experimentation with salt iodization for iodine deficiency took place in Europe in the early 1900s, the first large-scale trials were carried out in the US in 1916, and the first mass prophylaxis started in Michigan in 1924. The success of these efforts, along with improved economic standing, dietary diversification and use of iodophors in food

https://doi.org/10.1017/S0031182000007150 Published online by Cambridge University Press

processing have led to a dramatic reduction in iodine deficiency in industrialized countries. Following recognition of the sub-clinical effects of iodine deficiency on mental development, its high prevalence in Asia and Africa, and the joint advocacy by WHO and UNICEF, elimination of iodine deficiency was established as a *global* goal, with universal salt iodization as the key intervention. The 43rd World Health Assembly in 1990 established the year 2000 as the goal for elimination of iodine deficiency as a public health problem. This was followed by the World Summit for Children which generated commitment from 159 countries to develop plans of action for the elimination effort.

In the past decade, this global effort has been extraordinarily successful. Prior to this effort, many countries reported prevalences of iodine deficiency as high as 50 % in highly endemic areas, as measured by goitre rates or low median urinary iodine levels in the populations studied. Currently, most countries report dramatic reductions in prevalence, and equally dramatic increases in household use of iodized salt. In India, for example, the production of iodized salt increased from 0·5 million tons in 1985 to 2·8 million tons in 1992–3, with the capacity for iodization currently reaching 6 million tons (Hetzel & Pandav, 1997). Similarly, in Nepal, where logistic constraints are significant, the recent National Micronutrient Survey estimates the household use of iodized salt to be over 90 %. UNICEF estimates that 66 % of all the edible salt in the world is now iodized.

It should be noted that salt iodization is not the only intervention for iodine deficiency. With the recognition of the effects of iodine deficiency on cognition, and with many highly endemic communities identified with very high numbers of cretins being born, rapid administration of iodine was necessary. A single intramuscular injection of 480 mg of iodine in oil was found to protect against deficiency for at least 3 years. With concerns about HIV/AIDS, injections gave way to oral iodized oil which provides protection for about a year and which is still used today in some countries.

Whether with injections or oral capsules, the experience with iodine supplementation is informative. Most countries using injections required special mobile teams to cover the defined endemic areas. Since many countries did not have either the resources for such specialized teams or adequate health infrastructures to administer the injections, these programmes were costly and difficult to sustain. Programmes using oral preparations were simpler and could use lower level village workers. Since oil preparations are pharmaceuticals, there was no special legislation needed as there was for salt iodization and cost estimates were similar if the health infrastructure was strong enough. Consideration was given to tagging iodized oil capsules to immunization programmes. In spite of these advantages, supplementation programmes have been difficult to sustain and where they remain, they are used primarily for remote, highly endemic areas. With the recognition that sub-clinical iodine deficiency is more widespread than the earlier defined 'goitre endemic' areas, such supplementation programmes are now seen primarily as emergency measures to be used until an effective salt iodization programme is in place.

The increase in use of iodized salt and the dramatic reduction in iodine deficiency have been the outcomes of major national efforts that have been accomplished through close partnership between governments and the salt industry. Whether salt production is private or quasipublic, whether iodized salt is produced in-country or imported, this cooperation has resulted in successful supplies of adequately iodized salt to most households in most countries.

The experience with salt iodization serves as an example of successful cooperation between health authorities and the salt industry, and it can be useful when DEC-fortified salt is considered for inclusion in the intervention strategy for filariasis. Several aspects of the salt iodization experience may be helpful for DEC salt programmes: (1) The normal channels of salt production and distribution were used, with simple substitution of iodized salt for non-iodized salt. Programmes that 'medicalized' iodized salt and attempted to have iodized salt distributed through health channels were not sustainable. (2) Salt industry representatives were included early in discussions on the development of legislation and the regulatory environment that would affect them when they began salt iodization. (3) High-level multi-disciplinary advocacy efforts created a positive climate for salt iodization, and helped ensure demand for iodized salt. (4) Governments, with assistance from donor agencies, commonly subsidized capitalization costs, and continue to assist with procurement of potassium iodate to allow iodized salt to replace non-iodized salt without significant initial increases in cost to the consumer. (5) Governments also assisted with consumer education to help build awareness about iodine deficiency and demand for iodized salt. In addition, governments have completed knowledge, attitude and practice surveys on consumer preferences for packaging, unit size, and other product issues. (6) Monitoring measures were simplified so that the iodine content of salt could be easily measured during production and at the wholesale, retail and consumption level. Currently a simple test solution is widely used that causes salt to turn blue when it contains iodine. (7) Regional meetings were held to facilitate cooperation among countries on issues such as government standards, importation requirements, quality assurance, and other regional issues.

A COMPARISON OF IODIZATION WITH DEC-FORTIFICATION OF SALT

There are certain potentially important differences between a national salt iodization effort and inclusion of DEC salt as an intervention for filariasis. First, salt iodization programmes have been 'universal', in that they have been designed to cover entire national populations. Many countries require salt iodization by law and most have clear regulations governing the iodization process. Since filariasis is not necessarily universally distributed in countries but rather may occur in endemic pockets, universal fortification may not be necessary and the effort may be considered only for the defined endemic areas. This difference could affect the interaction with the salt industry, from a 'simple' substitution of iodized salt for non-iodized salt production to the production of special batches of salt fortified with iodine and DEC that are designed for distribution to specific endemic areas. This change would also have implications for educational efforts and creation of demand.

Second, iodine is well accepted as an essential nutrient while DEC is seen as a pharmaceutical. This may raise questions about the laws regulating use of pharmaceutical agents, particularly as food additives. Although the safety of DEC is well established, as it is for iodine, there remain those within the medical profession who may question population-based distribution, as happened early in salt iodization efforts. These issues have for the most part been addressed for salt iodization through close work with various medical groups, through political advocacy and through inclusion of more extensive information on iodine deficiency disorders (IDD) in various educational curricula, including curricula in the medical fields.

Third, there may be transient side-effects following the introduction of DEC salt, especially in areas with brugian filariasis. Therefore, solid education campaigns will be required to ensure understanding and prevent poor compliance in such communities before adequate consumption of DEC-fortified salt can be assured.

Fourth, there are cost implications for purchasing DEC for salt fortification. With salt iodization, UNICEF and other donor agencies either covered the cost of potassium iodate or subsidized its purchase, at least for the early part of the national effort. Since endemic filariasis exacts substantial costs from society, both the mass-treatment campaigns and the DEC salt interventions are very cost effective. However, for filariasis control efforts, there is currently no specific donor agency identified to cover these costs. Furthermore, national budgets for filariasis control are commonly small and already over-taxed. In addition, salt is a low-cost commodity and though purchased by nearly all populations, its profit margin is very small, thus making it more difficult for salt producers to cover these costs or to pass them on to the consumer.

Finally, and very importantly, salt iodization is a long-term strategy addressing a chronic problem whereas DEC-fortification is envisioned as a short-term strategy (1–3 years duration in any one community) aimed at eliminating transmission of LF. Thus, start-up costs will be a relatively greater proportion of total programme costs for DEC-salt usage, but the length of the programme will be much shorter and more clearly defined.

DEC SALT AS PART OF THE NATIONAL STRATEGY TO ELIMINATE LYMPHATIC FILARIASIS

What technical details need to be considered for including DEC-fortified salt in the national strategy?

Diethylcarbamazine (1-diethylcarbamyl-4-methyl-piperazine) produced as the dihydrogen citrate is a white powder that is soluble in water and very stable. The drug retains its efficacy through normal cooking procedures and is even stable through autoclaving (Hawking *et al*. 1950; Hawking & Marquez, 1967; Hawking, 1978). The compound does not have a strong taste and it has been shown to impart no changes in taste, colour or consistency when mixed with salt. No incompatibility has been demonstrated with the addition of DEC to salt fortified with potassium iodate. [A recent study at the University of Iowa (USA) specifically examined salt fortification with DEC and iodine. Potassium iodate and DEC were dissolved in water and the solution gradually applied to salt, using a manually operated spray bottle and continuous mixing in a low shear style (Hobart 140 QT planetary) mixer (similar to a small cement mixer). The salt was mixed until uniformly wetted, and then colloidal silicon dioxide was added with continued mixing until a free flowing powder was obtained. Batch sizes of 50 kg were successfully processed. This work provides evidence that the addition of DEC to the normal spray iodization processes commonly used for salt iodization is likely to result in salt that will provide adequate iodine and DEC.]

DEC is available in powder form from a limited number of manufacturers and currently costs approximately $24/kg, thus adding approximately $0·06 per kg of salt fortified at 0·25 % w/w, exclusive of equipment and labour costs. Based on the experience in India, WHO estimates that DEC salt fortification will add approximately $0·80 per year per adult to their annual cost for salt. It is estimated that in India economic losses from disability due to filariasis may approximate to $1 billion per year, making the additional expenses for a national filariasis programme well justified (WHO, 1997; Ramiah *et al*. 2000).

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Table 4. Daily and total DEC dose for different intervention strategies

Intervention strategy	Maximum daily dose per kg (mg/kg body wt) (for 70 kg adult)	Estimated total dose for the intervention (mg)
6 mg/kg body weight daily for 12 days	6	5040
6 mg/kg body weight single dose given once yearly	6	420
100 mg (adult dose) monthly for 1 year (12 doses)	1·4	1200
Salt with DEC @ 0·1 % w/w given for 6 months*	0·14	1800
Salt with DEC @ 0·2 % w/w given for 6 months*	0·28	3600
Salt with DEC @ 0·4 % w/w given for 6 months*	0·57	7200

* WHO estimates the average salt consumption to be 5–15 g/day/person. For this calculation, 10 g/person/day is used.

Fortification of salt with DEC is similar to fortification with potassium iodate and can be done through dry or wet mixing, although dry mixing may not yield an adequately uniform product. The machinery currently used for salt iodization can also be used for producing batches of DEC-plus-iodine fortified salt. As with iodine, it is important that there is adequate mixing time to ensure that batches produced have consistent amounts of DEC. There may be some differences in particle size between DEC and potassium iodate, and this may affect the settling time or rate at which DEC may move through salt. However, most countries now package salt in smaller plastic packages, thus decreasing the potential for settling.

Ideally, salt producers distributing to endemic areas would be requested to produce salt doubly fortified with DEC and iodine for the endemic population. Producers would substitute a pre-mix that would include a fixed amount of potassium iodate and DEC and would be given instruction on the correct mixing procedure. With the simple substitution of a DEC/iodine pre-mix for the usual iodine pre-mix, the fortification procedures would remain very simple, with little change from the single fortification with potassium iodate. Salt produced for endemic communities would, however, require different labeling.

What safety concerns are there with DEC salt for use by the general population?

There is extensive experience over the past 40 years with the use of DEC in mass treatment, with literally hundreds of millions of treatments administered. The original treatment for filariasis, which was very widely used, was 6 mg/kg of DEC given daily for 12 days, though a variety of different dosage regimens have been used. DEC in these treatment regimens has been shown to have 'low toxicity and to be safe for large-scale use in lymphatic filariasis' (WHO, 1992). Furthermore, DEC does not accumulate in the body and there is no evidence of chronic toxicity. Indeed, DEC has been used in mass campaigns and in salt fortification in large populations in several countries and these treated populations have included pregnant women. There is no report of any adverse effects on pregnant women from DEC salt use in these populations.

There can, however, be acute adverse reactions following treatment with standard doses of DEC and these appear almost exclusively in individuals with high microfilarial densities, especially in brugian filariasis. The reactions are generally transient and fall into two categories (Dreyer *et al*. 1994). First, there are systemic adverse reactions including headache, low-grade fever, joint pains and anorexia, among others, related to destruction of the microfilariae. Second, there are local reactions including lymph node tenderness and lymphangitis among others, which are caused by tissue inflammation around dying adult worms. These are the same localized reactions observed whenever adult worms die and thus they represent the normal response to successful treatment, rather than a toxic reaction to DEC. While these reactions are commonly mild and transient, there is always a concern that they may affect compliance for follow-up rounds of medication distributed during mass campaigns.

In contrast, following administration of DEC-fortified salt most studies have reported no side effects at all, though one recent study has described in detail mild, transient local reactions associated with DEC salt used in patients with brugian filariasis (Shenoy *et al*. 1998). Table 4 identifies the different DEC dosage regimens used in different treatment programmes, along with the total DEC dose received in each of these regimens.

How is DEC salt monitored to ensure adequate DEC in the salt?

For monitoring salt iodization, large producers use a titremetric method to determine the parts per million of iodine in batches of fortified salt. Titration provides a highly accurate estimate of iodine concentration. (Mannar & Dunn, 1995; May, 1996). There is also a semi-quantitative field test kit for testing iodine content in salt. This test involves

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application of a drop of a stabilized starch solution, and observation of the magnitude of the colour change, which reflects the concentration of iodine (Sullivan *et al*. 1995). Since the ratio of iodine to DEC will be fixed, testing for iodine can differentiate fortified salt from non-fortified salt. There are several laboratory methods to determine the concentration of DEC in food products, including colorimetry and chromatography. In addition, there is a field test method that has been widely used in China. The method uses bromo thymol blue, using 1–2 drops of 0·1 % solution mixed with a solution of 1–2 grams of salt in 5 ml of H_2O, which produces a colour change.

What information is needed before deciding whether DEC-fortified salt is appropriate for use in a country's filariasis elimination programme?

For areas without onchocerciasis or loiasis, WHO currently recommends either a dual-drug, single dose, annual mass distribution regimen; use of DEC-fortified salt; or some combination of these. It is estimated that the annual mass campaigns need to continue for 4–6 years, and the use of DEC salt for approximately 1 year, although these recommendations may change as more information becomes available. Therefore, in selecting the best intervention strategy, programme managers need to have: (1) specific knowledge of the distribution of filariasis in the country; (2) a realistic understanding of the capacity of the health infrastructure to mount a mass campaign; and (3) an understanding both of salt production and distribution and of the situation with regard to salt iodization.

Filariasis may be distributed in endemic pockets, with areas ranging from very high prevalence to areas where the population is not infected. This distribution is likely to be influenced by the distribution of the mosquito vector, the past establishment of infection within the communities and, in some areas, the degree of urbanization. Since the current recommendations favour mass distribution covering the entire population in endemic areas, these areas must be defined carefully. Furthermore, for salt programmes, understanding the distribution of filariasis is also important in order to identify those producers who normally supply salt to the specifically affected populations. The new rapid assessment techniques should make mapping the filariasis distribution much easier than previously.

There are significant human resource requirements for either a mass campaign approach or use of DEC-fortified salt. Recently, mass campaigns have been very successful for polio immunizations (National Immunization Days) and bi-annual high-dose vitamin A supplementation. Launching such a campaign, with the expectation of achieving over 75 % coverage, requires mobilization of a large number of people at the community level and building both awareness and support for the campaign among community members. This can be costly and can take a great deal of time both at the central level and before and during the campaign at the district and community levels. Since most countries have limited health staff for distal health facilities, there may need to be mobilization of teachers, community leaders and others to assist with the distribution. In countries with good results from National Immunization Days or vitamin A distributions, it may be easier to combine efforts or use a similar approach for filariasis endemic areas. Mounting such a campaign in the absence of this type of experience is likely to be more costly and to require more advance planning.

DEC salt programmes are likely to be most efficient if the normal channels of salt production and distribution are used rather than treating the DEC salt as a health commodity and attempting to distribute it through health channels. This has certainly been the experience with salt iodization, although in some instances, where there are just a few small endemic areas, it may not be unreasonable to provide the DEC salt through special channels. Thus, resources need to be mobilized to restrict the salt distribution to endemic areas and to work with the producers supplying these areas. There will be training needs, procurement and logistic supply issues to address, and cost issues to work through with producers. In addition, it will be important to establish a mechanism to assess coverage, with regard to both the adequacy of DEC in the fortified salt and the use of that salt in households in endemic areas. This monitoring process will require significant human resources until the process becomes routine, and even then, since market forces affect salt distribution, close monitoring will need to continue.

Clearly, for launching a DEC salt intervention programme it will be important to understand the relationship between the distribution of filariasis and the distribution of salt to populations inhabiting those endemic areas. For salt iodization, countries commonly perform a 'salt situation analysis' that reviews production capacity, quality, importation, cost, packaging and other aspects of salt. This analysis provides data on the market share for the larger producers, the number of smaller producers, and the patterns of distribution from producers to wholesalers to retail shops and finally to households. Much of this work centres around the need to know where to establish iodization units, and in most countries there is adequate consolidation of the industry to allow for a relatively small number of such units. In some countries, however, there are many smaller producers, and smaller iodization units are used for iodization.

Most countries are now achieving greater than 70 % coverage with iodized salt. If there is a salt

https://doi.org/10.1017/S0031182000007150 Published online by Cambridge University Press

Box 1. Essential questions in determining the appropriateness of DEC-fortified salt as an intervention for lymphatic filariasis in specific endemic areas

(1) Is there adequate government support for elimination of filariasis, and use of DEC-fortified salt?
(2) Are the areas endemic for filariasis clearly defined?
(3) Is there consensus among political leaders, members of the medical establishment, public health programme managers and representatives of the salt industry that DEC salt is an appropriate intervention – either alone, or in combination with mass distribution?
(4) Is there the ability to generate awareness and demand for DEC salt at the community level in endemic areas?
(5) Is the salt industry well organized, with known distribution patterns?
(6) Is there a national salt iodization effort, and is it successful?
(7) Is there an established monitoring system that ensures adequacy of salt iodine content during production and that can measure household coverage?
(8) Can the capacity to measure impact on transmission of LF using the new antigen of filarial DNA detection methods be established?

situation analysis that shows which producers distribute salt to endemic areas, then it may be relatively easy to work with those producers to produce doubly fortified salt for use by the endemic communities. On the other hand, if the supply to endemic areas is highly variable, from multiple producers, and changing over time, it may be more difficult to identify the appropriate producers with which to work. These factors, along with the adequacy of the iodization effort, status of the fortification equipment, and government policies and regulations regarding DEC all will affect the ease by which a DEC salt effort can be mounted.

What are the situations in which DEC salt might be an ideal intervention?

The ideal circumstances in which a DEC salt intervention strategy could be established most easily would include the following (see Box 1): (1) Salt iodization would be well established, with the bulk of production done by 2–3 large producers with modern iodization equipment and a good working relationship with the government. (2) The salt iodization programme would have a strong monitoring system both at the level of production (done by the producer) and at the wholesale, retail and consumer levels (done by the government). Results of this system would indicate that salt reaching the consumer consistently contained adequate iodine, thus meeting government standards, and that more than 80 % of households were consuming this salt. (3) Salt would be sold in 1 kg packages with labeling indicating that the salt is iodized. (4) Government food and drug regulations would allow fortification of salt with DEC without requiring a complex legislative or regulatory change. (5) Both the political environment and the clinical health establishment would view the current iodization effort favourably, and would also view fortification of salt with DEC for endemic areas favourably, without inappropriate concern that such an intervention would be dangerous. (6) There would be multi-sectoral support for such an initiative, with senior political leaders aware of the magnitude of the problem and supportive of interventions for elimination. (7) There would be the capacity, at community level, to generate awareness and understanding about filariasis, to generate demand within the communities for DEC-fortified salt, and to include in the overall programme a mechanism to address clinical cases. (8) There would be support from within the government or from a donor agency to cover the additional costs to producers to fortify salt with DEC. This might include subsidy of the DEC itself and of some additional staff to perform procurement and monitoring duties related to the selective distribution of DEC salt to endemic communities. (9) There would be good experience with other mass campaign interventions that would allow rapid establishment of a single dose annual dual drug distribution for filariasis to complement the salt effort, should this combination be chosen. (10) There would be an established cadre of health or other workers to perform monitoring at the district or community levels, and an established health information management system that could be used to aggregate these data for monitoring purposes.

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