The Role of Salt in Global Elimination of Lymphatic Filariasis

R Houston [a], M Lapointe [b], P Lammie [b], A Freeman [b], and D Addiss [b]

[a]PO Box 613, Bozeman, Montana 59715

[b]Division of Parasitic Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Fortification of salt with the medication diethylcarbamazine (DEC) may prove to be a critical intervention for the elimination of a devastating mosquito-transmitted parasitic disease of the tropics caused by a small thread-like worm (filaria). Lymphatic filariasis, which causes hydrocele and the gross deformity of the legs called 'elephantiasis', is ranked as the second leading cause of disability worldwide [1]. The recent development of new diagnostic and therapeutic tools has led to the recognition that lymphatic filariasis, along with other diseases such as polio, can be eliminated. Currently, the recommended strategy for achieving this goal is annual treatment of everyone in affected communities once a year with DEC or other effective drugs. This mass treatment with DEC reduces the levels of parasite in the blood (microfilaremia) to the point where mosquitoes can no longer spread it from person to person.

Because of the difficulties in distributing DEC tablets, particularly in urban areas, DEC salt has attracted increased interest among filariasis control officials in recent years. DEC is a good fortificant because it is tasteless, odorless, and extremely heat-stable. As an adjunct to mass distribution of DEC tablets, DEC salt has been used extensively in China, where transmission of the parasite has been essentially eliminated. DEC salt has also been studied extensively in India, Brazil, Haiti and Tanzania, with these studies confirming its safety and cost-effectiveness [2]. DEC salt delivers a very low dose of DEC (usually 0.2-0.4 % w/w) and is substituted for normal household salt for a minimum of 6-12 months, with close monitoring for the following 4-5 years. For the most common strain of filariasis, responsible for 90% of human lymphatic filariasis worldwide, no side effects have been reported from this intervention, and with the dramatic reduction in microfilaria in the blood, the transmission cycle is broken.

Outside of China, DEC salt has not been widely accepted primarily because of the limited experience of public health professionals in working with the salt industry. In the past decade, the global effort to eliminate iodine deficiency through salt iodization has been extraordinarily successful. Most countries now report dramatic increases in household use of iodized salt and rapid reductions in iodine deficiency prevalence. UNICEF estimates that 66% of all the edible salt in the world is now iodized [3]. This dramatic success of salt iodization is the result of a dynamic, positive collaboration between the salt industry and the public health community. In light of the recently announced goal of the World Health Organization to eliminate lymphatic filariasis globally, it is now time to build on the success of salt iodization by fortifying salt in filariasis-endemic areas with both DEC and potassium iodate. This can be easily done by adding a measured amount of DEC to the potassium iodate premix. In many areas of the world, salt fortification is likely to be the crucial strategy for successfully eliminating the scourge of lymphatic filariasis from the face of the earth.

1. INTRODUCTION

The second leading cause of permanent disability worldwide is a little known disease called lymphatic filariasis, according to The 1995 World Health Report [1]. The World Health Organization estimates that 1.1 billion people are at risk of getting this forgotten disease, with an estimated 76 million severely disabled. Lymphatic filariasis is distributed throughout the poorer tropical and sub-tropical countries of the world. It is present in over 70 countries: 38 in Africa, but with the largest affected population in Southeast Asia [4]. Lymphatic filariasis does not directly cause large numbers of deaths, nor does it cause dramatic epidemics. Instead, it becomes established in communities where it causes severe disability, social isolation and suffering among generations of those infected. It is capable of causing dramatic deformity of the legs--elephantiasis--and of causing painful hydroceles and other genital damage in a large percentage of infected men.

Rather than affecting whole populations, the disease becomes firmly established in specific areas, leaving adjacent areas unaffected. The infection is spread by mosquitos of various species which pass infective

larvae on to humans during a blood meal. These larvae migrate to the lymphatic system in the human host where they mature into adult worms, mate, and produce numerous tiny worms called microfilaria. These circulate in the blood, and are ingested by mosquitos in which they mature to infective larvae to complete the cycle. Unlike malaria, it is not easy to become infected--it usually takes chronic exposure to bites from infected mosquitos. Adult worms can live for 4-6 years and are prolific in production of microfilaria and it is this constant source of microfilaria that helps establish the infection in areas with the right species of mosquito for transmission.

But there is hope for the future for this overlooked disease. Improved diagnostic techniques, better understanding of disease and disease transmission, and simplified treatment and preventive measures may make it possible to eliminate certain diseases from the long list of those that affect humans. Ever since the eradication of smallpox in 1976 public health workers have nurtured the hope that this success could be repeated for other diseases. Recent intensified efforts against polio are encouraging, with no new cases reported in the Western hemisphere for the past 4 years. The characteristics of a disease, its transmission, and the dynamics of prevention and treatment are critical in considering whether a disease could be eliminated, and of *all* the diseases affecting humans, only 6 are being seriously considered. Lymphatic filariasis is one of these six. The 50th World Health Assembly in 1997 identified elimination of this disabling disease as a public health priority [1].

2. GLOBAL ELIMINATION

The attempt to eliminate this infection will rely on breaking the cycle of transmission through treatment of populations in areas with infection. Recent recognition of the severity of the problem along with the evolution of new diagnostic and treatment tools make it much easier to identify where the disease is established, and to break the cycle of transmission. Reduction in the number of circulating microfilaria in the human host prevents development of infective larvae in the mosquito, thus interrupting transmission to others. Since transmission to the human host from mosquitos does not occur with every bite from an infected mosquito, and since humans are the only reservoir for the most common form of lymphatic filariasis (*Wucheria bancrofti)*, interruption of transmission may not be required for more than a few years to reduce dramatically the likelihood that the parasite can maintain itself in a community.

There are several new approaches to breaking the cycle of transmission. Historically, individual cases were identified and treated with a multi-day medication regimen. Recently, treatment of entire populations in endemic areas, with a single dose of a combination of drugs (including albendazole, ivermectin and DEC) has been shown to reduce microfilaremia dramatically. This mass treatment of the entire population for a relatively short period can reduce microfilaremia below the point where transmission is likely, within the affected community.

While the mainstay of treatment is annual dosing with a combination of drugs, a decade of experience with salt iodization has revived hopes for another successful fortification program. A small amount of diethylcarbamazine or DEC (one chemical used as a medicine in treatment) can be added to salt with the benefit of preventing this dreadful disease. Used in place of regular household salt over the course of 6 months to several years, 'DEC salt' has been shown to be very effective in reducing microfilaremia rapidly and as completely as mass treatment. The past decade of experience with fortification of salt with iodine for eliminating iodine deficiency provides a wealth of experience in working with the salt industry on such a public health endeavor.

3. DEC SALT IN THE ELIMINATION EFFORT

Diethylcarbamazine has long been known as an effective drug for lymphatic filariasis, and was studied as a filaricidal agent as early as 1947 [5]. 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 Frank 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 [6]. This landmark study established DEC fortified salt as an additional intervention for filariasis elimination efforts.

3.1. Safety of DEC salt

There is extensive experience with DEC in mass treatment, which originally used a very large dose (6mg/kg/day) given for a 12 day period. This regimen was considered by WHO to have "low toxicity and to be safe for large-scale use in lymphatic filariasis" [7]. DEC does not accumulate in the body, and there is no evidence

for chronic toxicity. Adverse reactions with DEC are reported, and well documented for drug treatment programs, even using the single dose regimen. The most common *systemic* adverse reactions are headache, dizziness, pain in muscles and joints, and nausea, with or without fever. In addition, there are *local* adverse reactions that include pain and tenderness of lymph glands or of the scrotal area in men, and occasional abscess. These adverse reactions appear to be related entirely to the destruction and death of the microfilaria and adult worms respectively and as such, are almost unavoidable with drug treatment doses.

The situation for DEC salt is different in that this intervention provides a very low dose of DEC over a longer period. The amount of DEC in salt has ranged from 0.1% weight for weight (w/w) to 0.6% w/w. Based on research done in preparation for salt iodization, UNICEF and WHO report an average salt consumption of 10 grams per person per day [8]. This would result in a dose of 0.28 mg/kg body weight if that person consumed 10 grams per day of DEC salt with 0.2% w/w (substantially less per kilogram than the current drug treatment regimen). With the lower drug dose in DEC salt interventions, adverse reactions are rarely reported. In a review of the literature, adverse reactions were reported only for programs against the less common brugian filariasis, with none reported for bancroftian filariasis. DEC salt also has an extensive history, with the largest population interventions using DEC salt being in China, where an estimated 194 million people have used DEC salt in place of regular table salt. The experience in both mass campaigns and in salt fortification in large populations has included pregnant women, and there is no report in the literature on any adverse effects on pregnant women, and no reports of any long term adverse effects from DEC salt interventions.

Resistance to antibiotics develops quickly in bacteria, but is a much less serious problem for parasitic diseases with complex life cycles. Resistance to DEC for lymphatic filariasis has not been demonstrated, although some individuals may require several treatment courses to show evidence of destruction of all the adult worms. In theory, a chronic low dose of an antimicrobial could increase the risk of the development of resistance. However, this has not been demonstrated with the experience with DEC salt to date. The current feeling among expert groups is that development of resistance to DEC and other drugs used for lymphatic filariasis is not a major concern.

3.2. Effectiveness of DEC salt

Virtually all studies of DEC salt have shown positive results. DEC itself is known to be effective as a filaricidal agent, rapidly clearing microfilaria, and likely having an effect on the adult worm. As with mass treatment, there have been numerous studies on the use of DEC salt, studying different doses, different durations of treatment, and monitoring microfilaria prevalence and density as well as clinical findings and side effects.

The earliest studies were done in Brazil in 1967. These included work on the stability and biologic effectiveness of DEC in salt used for normal household use, including cooking. DEC is heat stable, and there was no reduction in effectiveness with normal use [6]. Larger population studies followed including those by Davis in Tanzania and by Sen and Rao in India. These studies showed reduction in microfilaria prevalence up to 90% following 6 months of DEC salt use [9,10,11]. 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 mass screening and treatment in the past, the microfilaria positivity rate had remained at 4.6%. As with the studies in India and Tanzania, microfilarial densities declined, with only 0.23% remaining positive after 6 months [12]. All of these studies involved intervention for *Wuchereria bancrofti* or bancroftian filariasis. None of the studies reported any significant side effects from the fortified salt intervention. Later studies in China in provinces where brugian or malayan filariasis (*Brugia malayi*) was endemic showed similar but somewhat less complete reduction, and some side effects were reported.

In the early 1990's, 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 island 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 microfilaria positivity to 0.0%, with the infection considered to have been eradicated from the island [13]. In a similar report, from Kinmen (Quemoy) Proper, initial mass distribution reduced microfilaria positivity substantially, but did not accomplish complete elimination. This was attributed to a relatively high rate of adverse reactions, affecting compliance with subsequent distributions. DEC salt was subsequently used for the entire population for 6 months, with follow-up surveys demonstrating complete elimination [13]. The successful elimination of lymphatic filariasis from the Quemoy islands was attributed in part to treatment of an entire isolated island population, reducing the risk of re-infection from infected mosquitos from adjacent communities in which the infection persists.

Several long-term studies have demonstrated that the initial reduction in microfilaria 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 reinfection. 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. As expected, however, these gains were lost after 8 years, with the recommendation being to cover the entire endemic population [14]. Similar work in several provinces in China, with multiple mass examinations, also shows encouraging results with persistently low positivity rates among the entire population treated as much as 10 years previously [15,16]. A summary overview of the Chinese program, which used various combinations of mass examination and treatment and DEC salt, suggests that DEC salt was critical in achieving elimination below 1% microfilarial prevalence for the country as a whole [17].

A follow-up study was done after the successful eradication of filariasis from the Quemoy Islands. This study 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 [18]. This underlines the importance of concurrent clinical treatment programs using the newer treatment regimens for elephantiasis, as part of the overall control program.

Finally, a study in Tanzania has compared four different DEC interventions over a 4 year period, reviewing both individual outcomes and community outcomes. This study again confirms that DEC salt is as effective as multiple day treatment, semi-annual single dose, and low monthly dose regimens [19]. These studies raised interesting questions about reinfection following intervention, showing clearly that individuals who have been microfilaremic are more likely to become reinfected. This suggests that in some individuals the treatment has not been adequate to kill the adult worm, or less likely, that some adults are immunologically more susceptible to repeat infections.

In summary, in studies from 1967 to the present, DEC 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 that there are advantages to DEC salt, including lower incidence of side effects, and possible better long term results perhaps from better compliance with DEC salt.

4. BENEFITTING FROM THE SALT IODIZATION EXPERIENCE

With its proven track record and lack of side effects, why has DEC salt not gained momentum as a critical intervention for elimination of lymphatic filariasis? The most likely explanation is that at the time of the early trials, the public health community had little experience in dealing with a commodity such as salt, and the concept of a health department distributing salt to populations was untenable. In the past decade however, a wealth of experience has been gained from the global effort for universal salt iodization. This experience is directly applicable from the fortification technology, to programmatic implementation, to monitoring and evaluation. It is the great success of salt iodization worldwide that presents an excellent opportunity to use DEC salt for elimination of lymphatic filariasis.

As late as the early 70's most countries did not iodize salt, or if they did, household use was low. Following additional studies on iodine deficiency that clearly demonstrated the effect on the developing brain, intensified global efforts to eliminate deficiency were begun. In 1990, the 43rd World Health Assembly 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 [20]. 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 goiter rates or low median urinary iodine levels in the populations studied. Currently, most countries report dramatic reduction in iodine deficiency, stemming from increased 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 [21]. Similarly, in Nepal, where logistic constraints are significant, the recent National Micronutrient Survey estimated 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 [3].

This remarkable success has established the capacity to fortify salt in most countries, with the ability to distribute the fortified product to most of the population. A great deal needed to happen to achieve this success. Countries had to understand the salt production and distribution pattern; governments had to work closely

with the usually private salt industry; government legislation and regulations needed review and revision; laboratory capacity needed to be reviewed and monitoring systems needed to be established. More specifically, iodine programs were successful in part because:

- the normal salt productions and distribution channels were used--the government did not attempt to produce or distribute iodized salt as a separate medical product.
- salt industry representatives were included early in discussions, including those establishing the regulatory environment
- high level advocacy efforts were included each step of the way
- equipment capitalization costs were subsidized (by governments and donor agencies) to limit price increases to the consumer
- governments assisted with education efforts to help increase demand for iodized salt
- simple monitoring methods were developed and used to highlight progress
- regional meetings helped establish cooperation among neighboring countries and helped address border issues

The technology for fortification is simple. Simple fortification units of varying capacity consist of a means of adding the fortificant, mixing the fortificant with salt, and conveying the fortified product to a packaging unit. Salt iodization has been done with units as small as hand cement mixers, to units with a capacity of 15 tons per hour. A spray or dry mix method is used, and the product is packaged (often by hand), usually in 1kg polyethylene bags with appropriate labeling [22]. This process has often resulted in greater attention to washing and consistency of crystal size, resulting in a transition toward a higher quality product more acceptable to consumers.

This entire process, of establishing salt iodization, has changed the environment in which deliberations are occurring about incorporating DEC salt into national programs. With regard to the technology of adding DEC to iodized salt, DEC has been shown to impart no changes in taste, color or consistency when mixed with salt. No incompatibility has been demonstrated with the addition of DEC to salt fortified with potassium iodate, and the process of fortification is the same. In fact a pre-mix with both DEC and potassium iodate can be substituted for the potassium iodate premix with some minor adjustments. Salt production and distribution patterns are known in most countries, and it should be easy to determine the patterns for areas with lymphatic filariasis. Producers are already familiar with fortification, and are likely to be willing to double-fortify provided their liability (financial and otherwise) is limited. Governments and donor agencies have experience with launching both advocacy efforts and education campaigns to make this effort acceptable to politicians and consumers. Monitoring systems, though sometimes weak, are in place to determine both salt iodine content, and household use. If DEC is added in a fixed ratio to iodine, these systems may be directly applicable, with only periodic checking of DEC content required.

There are some differences between salt iodization and DEC salt as public health interventions. First, salt iodization is universal--all salt is iodized in most countries--and will continue indefinitely, while DEC salt may need to be directed toward populations at risk, and is only needed for 4-5 years. Second, iodine is classified as an essential nutrient while DEC, even in such low doses, is classified a pharmaceutical. Although the safety of DEC is well established, this may raise concerns, and has regulatory implications. Finally, there are cost implications for adding DEC to salt. For salt iodization, UNICEF was a major donor helping governments with the cost of potassium iodate. Currently there is no such donor group to help with costs for DEC.

5. CONCLUSIONS

Lymphatic filariasis is now recognized as a major cause of disability worldwide, and is one of a small number of diseases targeted for elimination. Due to improvements in population assessment techniques, clinical treatment regimens and simplified interventions, the likelihood for success in elimination is vastly improved. The approach used has shifted from individual case identification and treatment to identification of endemic areas and treatment of populations at risk. This population-based treatment increases the likelihood of decreasing the spread of lymphatic filariasis among those living in areas of risk.

Several drugs are very effective in breaking the cycle of transmission, principally through reduction in microfilaremia. New single dose multi-drug regimens are known to be effective, and are much simpler to administer than earlier multi-day regimens. In addition, the dramatic progress made in salt iodization has created an opportunity to use DEC fortified salt as a key intervention to complement mass dosing. DEC salt is safe, easily added as a fortificant during salt iodization, and stable under field conditions, with no difficulties with taste,

color or acceptability by the consumer. In areas with bancroftian filariasis, no side effects have been reported with the use of DEC salt, and those reported in brugian filariasis areas have been mild. Finally, DEC salt has been shown to be as effective as mass dosing, when used as a substitute for normal household salt for as little as six months.

REFERENCES

1. World Health Organization, Lymphatic filariasis: reasons for hope. WHO/CDT/FIL/97.4. Rev.1. (1997).
2. D.W. Meyrowitsch and P.E. Simonsen, Long - term effect of mass diethylcarbamazine chemotherapy on bancroftian filariasis: results at four years after start of treatment. Trans Royal Soc Trop Med Hyg 92: 98-103, (1998).
3. N. Dalmiya, UNICEF, personal communication, (1998).
4. World Health Organization, Report of a Consultative Meeting held at the Universiti Sains Malaysia, Penang, Malaysia, Lymphatic filariasis infection and disease: control strategies. WHO(TDR)TDR/ CTD/ FIL/ Penang/ 94, (1994).
5. F. Hawking, P. Sewell, and J.P. Thurston, The mode of action of hetrazan on filarial worms. Brit J Pharmacol 5: 217-238, (1950).
6. F. Hawking, and R.J. Marques, Control of bancroftian filariasis by cooking salt medicated with diethylcarbamazine. Bull World Health Organ 37: 405-414, (1967).
7. World Health Organization, Lymphatic filariasis: the disease and its control. WHO Technical Report Series 821, (1992).
8. World Health Organization, Recommended Iodine Levels in Salt and Guidelines for Monitoring Their Adequacy and Effectiveness. WHO/NUT/96.13, (1996).
9. A. Davis and D.R. Bailey, The effect of salt medicated with diethylcarbamazine in bancroftian filariasis. Bull World Health Organ 41: 195-208, (1969).
10. A.B. Sen , R. Chandra, J.C. Katiyar and S. Chandra, Diethylcarbamazine medicated salt in the chemotherapeutic control of filariasis due to Wuchereria bancrofti in an open community. Indian J Med Res 62: 1181-1189, (1974).
11. C.K. Rao, R.M. Sundaram and P.K. Rao et al, Control of bancroftian filariasis with diethylcarbamazine medicated salt in open communities in rural and urban areas. J Commun Dis 8: 193-202, (1976).
12. Department of Filariasis, Provincial Institute of Parasitic Diseases, Shantung, Field trial on control of bancroftian filariasis using common salt medicated with diethylcarbamazine. Chin Med J 2: 365-371, (1976).
13. P.C. Fan, Eradication of bancroftian filariasis by diethylcarbamazine-medicated common salt on Little Kinmen (Liehyu District), Kinmen (Quemoy) Islands, Republic of China. Ann Trop Med Parasitol 84: 25-33, (1990).
14. P. Krishnarao, K. Raminder and T.K. Ghosh, Long term effect of diethylcarbamazine medicated common salt on bancroftian filariasis. J Com Dis 23: 128-130, (1991).
15. C. Zhong and T. Zhen, Control and surveillance of filariasis in Shandong. Chin Med J 104: 179-185, (1991).
16. J. Lui, Z. Chen, X. Huang and T. Zhaoping, Mass treatment of filariasis using DEC-medicated salt. J Trop Med Hyg 95: 132-135, (1992).
17. S. De-Jian, Filariasis control in the People's Republic of China, use of DEC-medicated salt as a major strategy. Working paper, Chinese Academy of Preventive Medicine, (1994).
18. P.C. Fan, H.W. Peng and C.C. Chen, Follow-up investigations on clinical manifestations after filariasis eradication by diethylcarbamazine medicated common salt on Kinmen (Quemoy) Islands, Republic of China. J. Trop Med Hyg 98: 461-464, (1995).
19. D. W. Meyrowitsch and P.E. Simonsen, Long - term effect of mass diethylcarbamazine chemotherapy on bancroftian filariasis: results at four years after start of treatment. Trans Royal Soc Trop Med Hyg 92: 98-103, (1998).
20. UNICEF, First Call for Children: World Declaration and Plan of Action from the World Summit for Children, UNICEF, (1990)
21. B. Hetzel and C.S. Pandav, SOS for a billion, the conquest of iodine deficiency disorders. Oxford University Press, Delhi, India, (1997).
22. V. Mannar and J. Dunn, Salt Iodization for the Elimination of Iodine Deficiency, International Council for Control of Iodine Deficiency Disorders, (1995).