CHARITY ENTREPRENEURSHIP

SALT FLUORIDATION TO PREVENT TOOTH DECAY

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CONSIDERED

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Executive summary

Tooth decay, also known as caries or cavities, is the most common health condition globally, affecting around 2.5 billion people. Thanks to the use of fluoride toothpaste and advances in dentistry, great improvements to oral health have been achieved in the developed world in the past several decades. However, preventive oral health has been hugely neglected in low-and middle-income countries (LMICs), and restorative interventions tend to be too expensive for their inhabitants to afford. As a result, many communities suffer from high rates of untreated tooth decay, leading to severe pain and decreased quality of life.

The cheapest way to prevent tooth decay and the suffering associated with it, is to ensure that people's teeth are exposed to sufficient levels of fluoride, which helps to strengthen and protect the enamel on the surface of teeth. Fluoridation of drinking water, practiced by countries such as the United States and (parts of) the UK, can be done for as little as $0.50 per person, per year, and has been demonstrated to reduce the rate of tooth decay by around 25%. However, water fluoridation is not feasible in places with underdeveloped water supply systems, and historically it has faced political opposition.

Brushing teeth with fluoride toothpaste has been a much more politically acceptable solution. However, fluoride toothpaste remains financially unaffordable in many parts of the world, with a year's supply costing several days' worth of workers' incomes. Additionally, tooth brushing behaviors are not very well established in many parts of the world, so interventions aimed at increasing access to fluoride toothpaste need to be paired with educational campaigns to increase tooth brushing. This makes such interventions quite complex and likely not cost-effective (though we note that we haven't explored this option in depth).

An alternative, which has been implemented in multiple European and Latin American countries (and, on small scales, in Africa and Asia), is adding fluoride to salt. This has multiple advantages: it is the cheapest intervention, costing less than $0.10 per person per year; it doesn't require advanced infrastructure; and virtually everyone consumes salt, so it is easy to reach high and consistent population coverage.

In this report, we explore whether incubating a charity focused on scaling up salt fluoridation would be an effective way of preventing the suffering associated with

tooth decay. Our evidence review has found that salt fluoridation is an intervention with a strong empirical support, with past studies indicating effectiveness on par with water fluoridation. The process of salt fluoridation, while varying between different types of salt-processing plants, is a relatively simple process that can be "tacked onto" existing salt iodization programs. We estimate that salt fluoridation can avert one DALY for $35.84[1] and add a WELLBY[2] for $10.24.

A charity working in this space would have to conduct multiple types of activities. First, it would need to conduct local feasibility studies to assess baseline exposure to fluoride (through drinking water, toothpaste, and other sources), and to map out the local salt mining, processing, and supply chains. It would need to provide technical support to salt-processing plants, to help them with installing fluoridation devices, procure the necessary chemicals, and set up systems for monitoring and quality control. Financial incentives may be needed to make the process cost-neutral for plants, as well as end users. Lastly, since any kind of fluoridation programs are essentially a mass medical intervention, they need to be run carefully in collaboration with the state and local governments, and educational campaigns may be necessary in order to get policymakers', health workers', and community buy-in.

While the intervention seems promising to us, and the activities are within the scope of what a typical fortification charity would do, we do have several concerns about it. Firstly, the case for its need in LMICs doesn't seem to be supported by the available data: Many LMICs currently have a low reported burden of oral diseases, either due to their low-sugar diets, or due to natural exposure to fluoride from groundwater. And while the "nutrition transition" toward high-sugar, low-fiber diets is happening in many countries, its effects on dental health are yet to be reflected in the data.[3]

Secondly, while salt fluoridation programs were introduced in many countries in Europe and Latin America in the second half of the 20th century, there have only been a few new programs in the past twenty years, most of which were/are, to our knowledge, limited in scale. As such, the acceptability of fluoridation in Asia and

[1] This is our estimate using adjusted/inflated disability weights (see section 7 for details). If we use the original disability weight from the Global Burden of Disease (GBD) study, we get a value of $179/DALY.
[2] Note: One WELLBY equates to a one-point change in life satisfaction on a 0-10 scale, per person per year. That means that a single person can gain multiple WELLBYs in a year if their life satisfaction improves by multiple points. As such, the measure is not well comparable with DALYs because their maximum value per year is 1.
[3] Though it is important to point out that data on dental health is scarce and often out of date, therefore not very reliable.

Africa remains somewhat uncertain, and it may be required to first invest resources into building international, state, and community buy-in.

Thirdly, while the evidence for the effects of salt fluoridation is strong, it mostly comes from a time period when HICs suffered a high burden of tooth decay. Its effectiveness nowadays – and in different regions of the world – may be smaller, owing to a lower burden of disease and potential exposure to other sources of fluoride. Conversely, the effects may be greater, as many LMICs today still have less access to restorative dental care than HICs fifty years ago. Some of these concerns are, unfortunately, difficult to assess from desk research, since little systematic international data-gathering has been done in the past two decades on the actual burden of oral diseases, exposure to fluoride, and oral health habits.

Lastly, and most importantly, there are concerns about potential negative health effects of ingesting fluoride. While the effects of excessive exposure are well documented – leading to disturbances in the tooth enamel and the formation of bones – the effects of exposure to low doses is controversial and hotly contested. In our view of the evidence, there is a non-negligible chance that exposure, to even small amounts of fluoride, during pregnancy and childhood may lead to neurological damage, with a potential population-wide reduction in IQ of one-two points. While the evidence in this space is largely of low quality, and may be highly biased, we find this risk of doing harm quite concerning.

The experts we spoke with all agreed that preventive oral health interventions are currently globally neglected. However, they highlighted that any programs need to be carefully designed and appropriate for local contexts, and that running a salt-fluoridation program in certain low-income countries could be quite challenging. They were hesitant to recommend salt fluoridation as an intervention that should definitely be introduced to new countries.

In summary, we think that salt fluoridation is a feasible intervention for a new small charity, and one that could cost-effectively prevent tooth decay in certain regions of the world. Based on our geographic assessment, we think that a charity focused on the West African region may be most likely to achieve high impact, due to its low groundwater fluoride levels, low use of fluoride toothpaste, and limited access to dental care. However, we have unresolved concerns about the potential negative health effects of exposure to fluoride, and would welcome seeing more conclusive evidence before setting up a charity in this space.

Overall, our view is that scaling up salt fluoridation in LMICs is not an idea worth recommending to charity founders at this moment.

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1 Introduction

This report has been produced by Charity Entrepreneurship (CE). CE's mission is to cause more effective charities to exist in the world by connecting talented individuals with high-impact intervention opportunities. We achieve this goal through an extensive research process and our Incubation Program. In 2022, our research process focused on the top highly scalable global health interventions.

Salt fluoridation to prevent tooth decay was chosen by CE research staff as a potentially promising intervention within this category. This decision was the result of a five-month process designed to identify interventions that were most likely to be high-impact avenues for future charity entrepreneurs. This process began by listing nearly 300 ideas and gradually narrowing down, examining them in more and more depth.

In order to assess how promising interventions would be for future charity entrepreneurs, we use a variety of decision-making tools such as group consensus decision-making, weighted-factor models, cost-effectiveness analyses, quality of evidence assessments, case study analyses, and expert interviews.

This process was exploratory and rigorous, but not comprehensive – we did not research all 300 ideas in depth. As such, our decision not to take forward a charity idea to the point of writing a full report should not be seen as a view that the idea is not good.

2 Background

2.1 The scope of this report

Nearly half of the world's population, an estimated 3.5 billion people, suffer from oral diseases. Dental caries (also known as cavities or tooth decay) affect around 2.5 billion people, making them the single most common health condition globally (WHO, 2022). These numbers are expected to further grow in the future, as developing countries experience the "nutrition transition" toward diets high in free sugars, and low in fiber (Reardon et al., 2021). While caries rarely lead to serious illness or death, they can cause severe pain if left untreated. And while treatment is usually readily available in high-income countries (HICs), dental care is usually either unavailable or unaffordable for people in low-and middle-income countries

(LMICs),[4] where the number of dentists per capita can be over 100 lower than in HICs, and where the typical expenditures on oral health are only $10 per person, per year, or less (Uguru et al., 2020; Righolt et al., 2015).

Increasing access to better dental care for those suffering from tooth decay is unlikely to be achievable in a scalable, cost-effective way, but prevention can be achieved extremely cheaply. Aside from limiting consumption to simple sugars – which may be achievable via policy interventions such as sugar taxes, or limiting the access to sweetened beverages (Teng et al., 2014) – up to 50% of caries are preventable by adequate exposure to fluoride, such as in the form of fluoride toothpaste or via fluoride fortification (Marthaler, 2013).

Despite this potential to avoid unnecessary suffering, preventive oral care has been hugely neglected for the last two decades (Benzian & Listl, 2022). Very few international organizations are focusing on it, and actors such as the World Health Organization (WHO) have scaled down or closed some of their programs (based on our expert interviews). There are likely several reasons for this neglect, including (i) the fact that oral diseases have a limited effect on mortality, thus not being a priority issue for the global health community; (ii) dental health being managed by separate national bodies than the rest of healthcare; (iii) weak incentives for dentists – most of whom are private professionals – to invest time and resources into preventive care (Benzian et al., 2011; Watt et al., 2019).

Despite the neglect of the past 20 years, now may be a timely moment to put resources into preventive oral care. In November 2022, the WHO released its Global Oral Health Status Report (WHO, 2022b) where it took stock of the current situation, including presenting data on diseases, health system challenges and opportunities for reform. It made the conclusion that the status of global oral health is alarming, and requires urgent action. The report is supported by the Global Oral Health Strategy (WHO, 2022c) and the Global Oral Health Action Plan 2023-2030 (WHO, 2023; both currently under development), which are expected to "provide unique and unprecedented opportunities for real change" (Benzian, 2021). In addition, work on defining Best Buys in Oral Health and other supportive work streams are underway (Benzian & Listl, 2022).

In the next section, we make the case that oral health is a large-scale issue from the perspective of human health and well-being, and provide an argument that fluoride

[4] As well as for many lower-income people in HICs

is instrumental in preventive care. After briefly exploring the other options, we focus on salt fluoridation as the intervention that seems most promising in terms of feasibility, scalability, and cost-effectiveness.

2.2 The scale of oral health problems and associated suffering

Dental problems are very common; more than 80% of people will have had at least one cavity by the age of 34 (CDC, 2022). The Global Burden of Disease study estimates that oral health conditions cause approximately 0.91% of global disability-adjusted life years[5] (DALYs). However, there are reasons to think that this value underestimates the severity of suffering caused by dental pain, since the disability weight given to toothache is only 0.01, which is the same value as mild acne. While this is plausible in cases of mild pain, Bettle (2022) found that the pain ratings for severe dental pain are comparable to migraine pain, which has a disability weighting of 0.441. Therefore, on top of looking at the DALY burden, we follow Bettle (2022) in also looking at pain and at the well-being loss it results in. We additionally estimate an "adjusted DALY burden", using our best estimate of the real disability toothache causes – see section 7 for details.

Dental pain is a very common health issue. In children, a meta-analysis estimated that 20% of under-5s and 40% of children aged between 6 and 12 have experienced dental pain (Pentapati et al., 2021). In adults, a meta-analysis (from mostly HICs) estimated the prevalence of dental pain at between 7-32% (Pau et al., 2003). Note, however, that there was large heterogeneity between studies, as well as regional heterogeneity within studies, so it is difficult to get an accurate and representative global value. A common finding is also that dental pain is more commonly experienced by individuals from lower socioeconomic classes (Pentapati et al., 2021). Synthesizing the available evidence, and discounting for possible biases in the data, Bettle (2022) estimates that around 30% of people in LMICs are likely to have experienced dental pain in the last year.

How severe is the suffering caused by dental pain? The evidence suggests that, in regions with limited access to dental care (i.e., much of the developing world), the pain is often severe (Bettle, 2022). For example, in a study from Iran, 43% of adults who reported having experienced dental pain in the preceding six months rated it as

[5] The DALY is a metric that combines the burden of mortality and morbidity (non-fatal health problems) into a single number. One year of life lost equals 1 DALY, while one year lived with a disability equals a value between 0 and 1, depending on the severity of disability. It is the primary metric used by the World Health Organization to assess the global burden of disease.

'severe' or 'very severe', 31% as 'intermediate', and 26% as 'weak' (Kakoei et al. 2013). In a study of school children in India, 40% of those experiencing dental pain rated it as severe, 43% moderate pain, and 17% mild pain (Saheer et al., 2015). Somewhat conservatively, this suggests that maybe 50% of those who experience dental pain would rate it as moderate or severe.

We can also look at the self-reported pain by patients who are actively experiencing dental pain and seeking treatment for it. In several studies that asked such patients to rate their pain on a linear 0-10 scale, such patients typically rated their pain as either in the 4-6 'moderate' region or the 7-10 'severe' region (Bettle, 2022) – consistent with the studies quoted in the previous paragraph. Note that this would place dental pain roughly halfway between the severity of migraines and lower-back pain (Sharma et al., 2020).

Lastly, we can get a sense of the severity of dental pain by looking at how much people are willing to pay to avoid it. Here, Bernabé et al. (2017) report that out-of-pocket payments for emergency dental care are among the main drivers of catastrophic health expenditures (defined as spending more than 40% of a household's capacity to pay). This suggests that people value averting dental pain very highly.[6]

In order to understand the total burden of dental pain, the last thing we need to understand is the typical duration of it. Bettle (2022) provides a detailed overview of the reasons why dental pain in LMICs may be much longer-lasting than that experienced in HICs. In summary, untreated dental decay tends to spread from the enamel on the outside of the tooth to the inner pulp where it causes swelling, which leads to swelling and an accumulation of pus, both of which cause pain. Without treatment, the swelling will eventually cut off the blood supply to the nerve and kill the tooth. In time, the swelling will go away, the pus will eventually drain and pain levels will typically subside. While the whole process may take from months to years, our best estimate is that an untreated cavity will result in a dead tooth within 6-12 months from the onset of pain (Boston Dental Group, 2022; Enamel Dental Centre, 2020).[7]

[6] Another negative effect of dental pain is school absence and lost productivity (Sheiham, 2005). In the interest of brevity, we do not explore these in detail in this report, but we encourage future researchers to take them into account.

[7] This is consistent with the value we obtained from the GBD database: The estimated number of "caries in permanent teeth" is 2,111,107 and their incidence is 2,908,075/year. This implies an average duration of 0.73 years

While a dead tooth will likely stop hurting, the health risks do not stop there. The infection in the pulp can spread to other tissues in the mouth, as well as travel through the blood system to other parts of the body, potentially causing a range of severe problems. These can include:

- Septic shock (Mannan et al., 2021)
- Cardiovascular diseases, including coronary heart disease, stroke, hypertension, and atrial fibrillation (Meurman et al., 2004; Chang et al., 2021; Munoz Aguilera et al., 2020; Vedin et al., 2015)
- Type 2 diabetes (Borgnakke, 2019)

Many of these links are, however, poorly understood. Even where they have been studied quantitatively, most evidence is correlational and it is therefore not clear how strong the causal relationship is between dental infections and these other diseases. For a detailed overview, we refer the reader to Bettle (2022).

2.3 Potential interventions

Tooth decay is the breakdown of teeth as a result of exposure to acids produced by bacteria in the mouth (Silk, 2014). These acids speed up the process of thinning of the tooth enamel, also known as demineralization. There are two ways of preventing caries from developing: slowing down the pace of demineralization, or speeding up remineralization, i.e., the process of enamel repair (Featherstone, 2008).

2.3.1 Limiting the consumption of sugar

The best way to slow down demineralization is to limit the consumption of simple sugars, as those are the primary energy source for the bacteria that cause caries (Touger-Decker and van Loveren, 2003). In their analysis of detailed data from Japan on the relationship between sugar intake and caries, Sheiham and James (2014) found a strong positive relationship between the two, with a 10pp increase in energy coming from sugar being associated with a tenfold increase in caries. The reduction of sugar consumption – especially from sugar-sweetened beverages – also has the additional benefit of reducing the risk of obesity and the diseases associated with it (Popkin & Ng, 2021).

One way to reduce the consumption of sugar is to educate the general public about the effects of sugars. Various versions of educational interventions have been tried in the past, including in-person education, distribution of materials (like pamphlets), and use of mass media (Vercammen, 2018; Ling et al., 2022). While

these interventions tend to be effective, we do not expect them to be scalable in a cost-effective manner in LMICs[8]. They will also likely be faced with opposing pressures from the sweetened-beverage industry, which has been growing its presence in LMICs: As of 2019, Coca-Cola had set aside $12 billion for marketing in Africa by 2020 and PepsiCo had set aside $12 billion for its operations in India (Peres et al., 2022). As such, we have deprioritized this approach in our research.

Another way to reduce the consumption of simple sugars on a societal level is to introduce a sugar tax. Such taxes – either on all added sugar or on sugar-sweetened beverages – have already been introduced by multiple countries in Europe, Asia, and the Americas. A meta-analysis shows that a price increase of 10% results in, on average, a 10% reduction in consumption of sugar-sweetened beverages (Teng et al., 2019). As such, they are an effective policy tool that we support expanding. However, sugar tax laws often face opposition from both the general public and the sugar industry, which limits their chances of success. Even some countries that previously successfully implemented them have since considered removing them (such as the UK; Narayan, 2022) or actually removed them (such as Israel; Troen, 2023). Since our current round of research is focused primarily on community interventions, as opposed to strictly policy interventions, we have also deprioritized this intervention.

2.3.2 Increasing exposure to fluoride

The other approach to preventing the development of caries is to support the process of tooth remineralization. This is a natural process through which minerals that had been partly dissolved by acids are returned to the surface of the tooth enamel. While the surface of teeth is normally made up of carbonated hydroxyapatite ($Ca_5(PO_4)_3OH$), when fluoride ions are present in the saliva, remineralization results in the crystallization of fluorapatite ($Ca_5(PO_4)_3F$), which forms more quickly and is more much more acid-resistant than ordinary hydroxyapatite (Li et al., 2014). Fluoride additionally acidifies the cytoplasm of bacteria and inhibits vital enzymes, thus having antibacterial properties (Aoun et al., 2018). This is why regular fluoride exposure strengthens the teeth and makes them less susceptible to caries.

There are two ways in which people can be exposed to fluoride: topically or systemically. Topical fluoride exposure methods include fluoride toothpaste, fluoride mouthwash, and fluoride varnishes and gels (usually applied by

[8] Though we note that we haven't evaluated them in detail in our research.

professionals). Systemic exposure – which essentially means fluoride being ingested – can happen via naturally fluoridated water (which is present in many parts of the world) or via artificial fluoridation programs, such as water, salt or milk fluoridation (O'Mullane, 2016). While it has long been debated whether both of these types of exposure are needed, it is now the expert consensus that the majority of the fluoride benefit comes from its topical contact with teeth, rather than its ingestion. However, fluoride is protective whether or not it is ingested, since even "systemic" fluoride comes into contact with teeth and remains dissolved in the saliva (Hellwig & Lennon, 2004; Sampaio & Levy, 2011).

The most common way of exposing the teeth to fluoride is daily brushing with **fluoride toothpaste**. This has been an extremely effective strategy (Twetman et al., 2009), and is credited for being responsible for the massive decrease in caries prevalence in Europe in the second half of the 20th century (Cheng et al., 2007). In fact, as shown in Figure 1 below, both countries that have implemented community fluoridation programs (such as water and salt fluoridation, discussed below) and those that haven't, have experienced comparable reductions in the prevalence of caries.

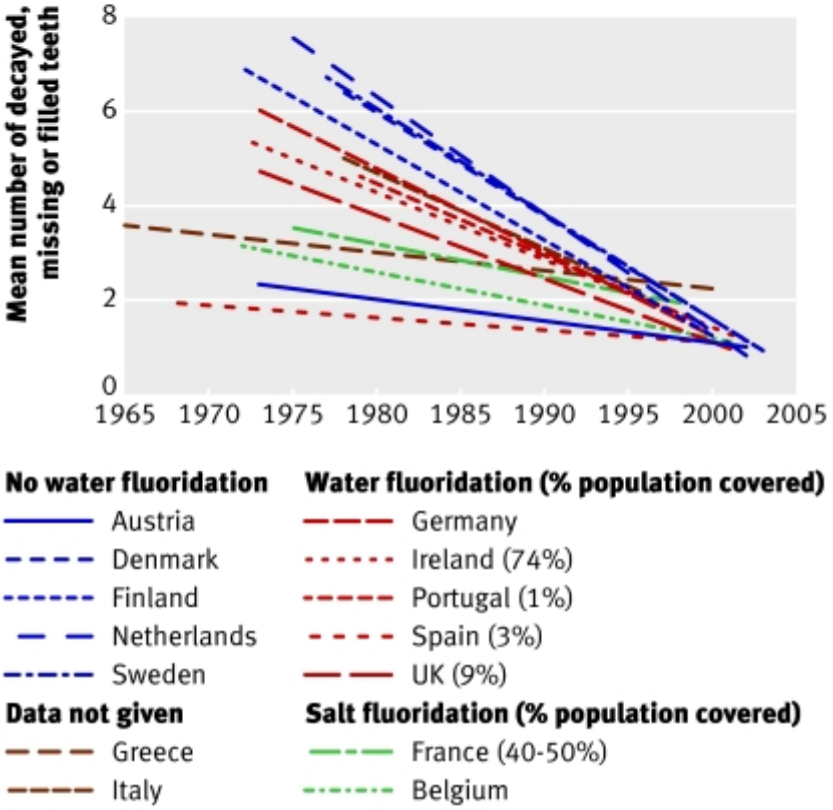

Figure 1: Prevalence of decayed, missing, or filled teeth in Europe, 1965-2005 (Cheng et al., 2007)

Increasing the use of fluoride toothpaste should therefore be a key long-term strategy for caries prevention worldwise. However, in the short term, we have multiple concerns about the feasibility of this idea:

- Fluoride toothpaste is currently not affordable in many LMICs (Gkekas et al., 2022). While interventions to improve its affordability have been proposed – such as reducing taxes on fluoride toothpaste, encouraging local production of generic, unbranded toothpaste, or encouraging differential pricing (Goldman et al., 2008) – most of these haven't been tested (to our knowledge), so we are uncertain about their feasibility, cost, and effectiveness.
- An intervention targeting the use of fluoride toothpaste may need to be paired with an educational intervention on how to properly brush teeth. While the self-reported prevalence of toothbrushing seems relatively high in many LMICs (Han et al., 2020), anecdotally (based on our expert conversations), there is still a big difference in the frequency and quality of oral hygiene habits between HICs and LMICs.
- While successful educational interventions have been tested in the past, they have relied on approaches such as in-person education (Coelho Leal et al., 2002), supervised toothbrushing (Kang et al., 2008) or digital training (Graetz et al., 2013). All of these seem either costly to scale, or not feasible in low-income countries.

As above, we have not exhaustively explored the potential interventions in the toothpaste space, and remain open to the possibility that there are cost-effective solutions. However, in the rest of this report, we will focus on fluoridation as the likely more feasible and cost-effective approach.

The most common method of mass administration of fluoride is the **fluoridation of drinking water**. It has been practiced by the USA for over 70 years, and currently covers about 63% of the country's population (CDC, 2020). The program has been deemed so successful that the CDC has listed it as one of its top 10 greatest public health achievements of the 20th century (CDC, 2015). It is also one of the key parts of the WHO's Oral Health Strategy, alongside fluoride toothpaste (WHO, 2022d). Compared to toothpaste, water fluoridation has been called the 'great equalizer' in dental health, as it overrides the effects of social deprivation and the associated decreased likelihood of toothbrushing (e.g., due to homelessness, mental health issues etc.; Toque and Kennedy, 2015).

However, there are also some serious downsides to community water fluoridation:

- The intervention relies on a quality piped water system, which is not available in many LMICs.
- Consumption of piped water can vary a lot between people, thus exposing the population to a very variable range of fluoride, potentially ranging from inadequate to excessive.
- While water fluoridation is a cheap intervention, costing about $1.26 per person per year in the USA (CDC, 2001), it is still somewhat wasteful. Only a small fraction of piped water is consumed, so the majority of the added fluoride chemicals are not utilized.
- There is a history of failed water fluoridation projects, including efforts in Guatemala, Jamaica, Panama, and Argentina. The most common reasons for discontinuation or failure to scale have been related to either running costs, or low coverage of piped water (Estupiñán-Day, 2005).
- There is a long history of opposition to water fluoridation, based partly on the fact that it "medicalizes" the most essential human nutrient without giving citizens an option to opt out (Aoun et al., 2018).

An alternative method of exposing a population to fluoride is to add it to **salt**. Salt has several advantages over water:

- It doesn't require advanced infrastructure (other than sufficiently advanced salt processing plants; see section 3.1)
- The process of salt fluoridation is technically very similar to that of salt iodization, meaning that the equipment and appropriately trained staff are already there (Marthaler et al., 2011)
- Essentially, everyone consumes salt, whether by directly adding it to dishes or by consuming food products that contain salt (such as bread)
- It is the cheapest method of fluoridation, since most salt produced in salt-processing plants is intended for consumption[9] (Gillespie & Marthaler, 2005)
- By offering fluoridated salt alongside non-fluoridated salt, consumers can be given a choice to buy the non-fortified version

Salt fluoridation has a long history. First trials began in the 1950s in Switzerland, and after promising results that indicated up to 50% reduction in caries (see section 5.1), its use spread to other countries in Europe, including Germany, France, and Switzerland, where between 30% to 80% of the marketed salt for domestic use is fluoridated (Gillespie et al., 2007). Many countries in Latin America and the

[9] 17.5% of all salt produced globally is for food uses (ref), though we expect the proportion to be even higher for processed salt.

Caribbean, as well as a handful in Africa and Asia, have also implemented salt fluoridation in the past (see section 4.1 for details). However, most of these programs were implemented in the second half of the 20th century, with very few new programs starting in the past three decades. To our knowledge, the main reason for this limited recent development has been a lack of prioritization for preventive oral health interventions, rather than any material arguments against the intervention.

As such, salt fluoridation seems like an effective, cost-effective, feasible, scalable, and neglected intervention. In the following sections, we explore each of these aspects in depth.

3 Theories of change

3.1 Barriers a charity may face

Even if we choose a country or area that has the basic prerequisites for benefitting from a salt fluoridation program – low groundwater fluoride concentration, low exposure to other sources of fluoride, high burden of dental caries, and limited access to dental care – there are still multiple barriers to salt fluoridation a charity may face:

1. Technological readiness

Salt fluoridation requires a certain minimum level of technological sophistication in the local salt processing industry. In general, there are three types of processes of transforming crude salt into table salt: refining, hydromilling, and the mill-and-package method. The former two are usually done at large, technically-advanced facilities, and produce salt with high purity and good consistency, making it suitable for fluoridation. The mill-and-package method, which requires the least machinery and which tends to be used by small-scale producers, produces the lowest-quality salt. Oftentimes, this process does not allow accurate and consistent enough addition of fluoride, making it unsuitable for fortification (Estupiñán-Day, 2005).

If such underdeveloped salt processing is common in a target country, the charity may need to work with the industry to upgrade their salt processing facilities (if that is deemed to be a cost-effective use of charity resources).[10] However, since the

[10] Note that a consideration here may be that, by investing in upgrading the technology to allow fluoridation, it may allow the facility to fortify their salt with other micronutrients – such as iodine, iron, or certain vitamins (see the Annex) – thus increasing the charity's impact

process of fluoridation is technically very similar to the process to the process of iodization – to the extent that premixes of iodide and fluoride compounds[11] are usually made – facilities that iodize their salt should be able to include fluoridation with minimal changes (Estupiñán-Day, 2005, O'Mullane et al., 2016). And since iodization is extremely common, with 88% of salt globally being iodized, including 85% in sub-Saharan Africa, we do not think that technological preparedness should be a major barrier (Zimmermann and Andersson, 2021; The World Bank, 2019).

2. Degree of centralization of salt production

A related barrier is the degree of centralization vs fragmentation of the local salt industry. While we have not been able to collate systematic data on this issue, there is certainly variation between different regions of the world. For instance, in Latin America, salt processing is highly centralized, with a single company (Morton Salt) controlling about 40% of the market and most salt processing being done in large facilities. Other countries, such as India, have several large companies that dominate the market, supplemented by a large number of small-and medium-sized businesses (based on our conversation with Shakun Sharma). Other regions, such as parts of Africa or Southeast Asia, may be made up mostly of small-and medium-sized processors.

An example of where this was previously an issue is Cambodia. In 2010 it attempted to introduce salt fluoridation, but the project was abandoned after a feasibility study indicated that the industry wasn't ready. This was particularly due to the existence of multiple salt processors with inadequate technology and poor quality assurance (Petersen et al., 2012).

3. Knowledge and beliefs about fluoride

Local beliefs about the risks and benefits of fluoridation may also be an issue. Historically, fluoridation – especially community water fluoridation – has faced various forms of opposition. This opposition has been based on concerns about its efficacy in preventing caries, its potential negative effects on health, and the view that fluoridation amounts to mass medication, removing people's freedom of choice (Carstairs, 2015; Fluoride Action Network, n.d.). Salt fluoridation seems more socially acceptable, due to the element of choice on the side of the consumer, but a charity in this space should still expect to have to justify its support of fluoridation, and dispel misinformation about its negative health effects. See section 8.8 for a detailed discussion of these effects.

[11] Typically, sodium iodide or potassium iodide for iodine and sodium fluoride or potassium fluoride for fluorine

There are at least two examples where beliefs about fluoridation proved to be a barrier. In India, which had considered introducing salt fluoridation, there was resistance from the health authorities due to concerns about effectiveness and safety of the intervention. Eventually, this prevented the program from starting (Petersen et al., 2012). In Lebanon, while the government was supportive and voted to introduce mandatory fluoridation in 2011, the decision stirred public controversy and resulted in the law not actually coming into effect (Aoun et al., 2018).[12]

4. **Insufficient baseline data on fluoride exposure**

While some past data exists on the likely population levels of exposure to fluoride in different parts of the world, much of this data is not granular enough or recent enough to be used to support the argument for local fluoridation. For instance, groundwater fluoride levels may vary significantly between different regions within a country, so while fluoridation may be beneficial in some areas, it may be harmful in others. As such, most past fluoridation programs had to be preceded by various local feasibility studies (see section 3.2 below).

3.2 Charity activities

We expect the charity to have to engage in a range of activities, some happening before a salt fluoridation program can be started, some during its set-up, and some once the program is running.

3.2.1 Prior to the program

Due to the general poor quality of aggregated data on fluoride, oral health, and the salt industry, the charity will need to undertake a series of feasibility tasks and studies in order to determine an area's suitability for fluoridation (Petersen et al., 2012; Estupiñán-Day, 2005; Pollick, 2013):

- Mapping out local concentrations of fluoride in water, to make sure fluoridated salt is not used in areas with concentrations above 0.7mg/l
- Identifying up-to-date data on the local state of oral health (such as the prevalence of untreated caries)
- Identifying the main producers, importers and exporters of salt
- Understanding the level of technological advancement of the local salt-processing industry, including whether salt iodization is already being done

[12] The controversy is documented by the fact that the government requested a rapid evidence review to inform the debate (Fadallah et al., 2015).

- Mapping out the local salt distribution network to understand where salt from given processing plants is being sold
- Mapping out the local patterns of salt consumption and deciding on which salt distribution channels to focus on – domestic salt, salt for meals at schools and large kitchens, salt for food items such as bread, etc.

Additionally, the charity should gauge the existing level of political and health authorities' will for undertaking a salt fluoridation program. While the charity itself can lead on many of the activities necessary for putting salt fluoridation in place (see section 3.2.2), government involvement will be necessary to ensure that the intervention follows local rules and regulations around fortification, and that its progress isn't hindered by government opposition.

3.2.2 Setting up a program

Once a suitable target location has been identified in terms of its potential benefit from fluoridation, technological readiness, and political will, the charity's main activities will consist of (i) technical support to the salt-processing industry, (ii) technical support for governments, and (iii) educational activities.

Firstly, the charity will need to work with the salt-processing industry in supporting them with the introduction of fluoridation in a way that minimizes the need for them to invest resources. This may involve technical assistance to include capacity-building on fluoridation methodology, setting up procurement for the necessary chemicals, and upgrading the plants' technology if needed. It will also be necessary to put in place at-facility surveillance technology and quality-control processes, to ensure that the produced salt is consistently fluoridated at the determined level.[13]

Next, the charity will likely need to provide technical assistance and guidance to countries on setting up and monitoring a fluoridation program. This may involve assistance with drafting necessary legislation for fortification,[14] setting up processes for epidemiological surveillance systems of salt fluoridation, and coordination between health agencies and salt producers. It is also recommended to try to embed dedicated staff in government agencies who are tasked with coordinating such activities (based on our conversation with Anne Wanlund from Canopie, previously Project Health Children). In the past salt-fluoridation programs

[13] For details on the technical aspects of introducing salt fluoridation, we point the reader to chapter 5 of Estupiñán-Day (2005)
[14] A blueprint for a legal framework for fluoridation is provided in chapter 9 of Estupiñán-Day (2005)

in Latin America, the Pan American Health Organisation (PAHO) found it beneficial to designate a "country technical officer" who was responsible for liaising between different stakeholders, coordinating consultant work dealing with project components under development, expediting the development of legal documents designed to enforce salt fluoridation, and generally being the main in-country point of contact (Estupiñán-Day, 2005).

Lastly, the charity should spend some resources on educational activities targeted at policymakers, healthcare providers, the salt industry, as well as the wider public (Marthaler et al., 2011). These activities have several aims:

- Disseminate information about the feasibility and benefits of salt fluoridation, to get government and industry buy-in
- Preemptively counter potential misinformation about fluoride
- Encourage the public to buy fluoridated table salt (while avoiding over consuming salt)
- By increasing demand for fluoridated salt, assure producers that there will be a market for their new product (and that they could even benefit financially if they were the first ones to offer it)

Note that the extent of required community education about the benefits of fluoride will depend on the distribution channels. If only table salt (for home use) is fluoridated, there will be a greater need for creating demand than if other kinds of salt (e.g., for use in schools or bakeries) are also fluoridated.

3.2.3 Ongoing support

The charity's activities shouldn't stop once a salt-fluoridation program has been put in place, as there will be a need for various kinds of ongoing technical support. This has been demonstrated by the case of Latin America, where multiple programs have suffered setbacks since PAHO ended its official program support there (based on our expert interviews). We expect there to be a need for:

- Technical support with quality at the salt-processing facility level
- Ensuring that facilities continue fortifying, either through technical support or via financial incentives (to offset the small but non-zero cost of fortification)
- Support to governments with monitoring compliance
- Maintaining systems for tracking the flows and sales of fluoridated salt within countries and across country borders
- Ongoing educational activities

3.3 Theory of change diagram

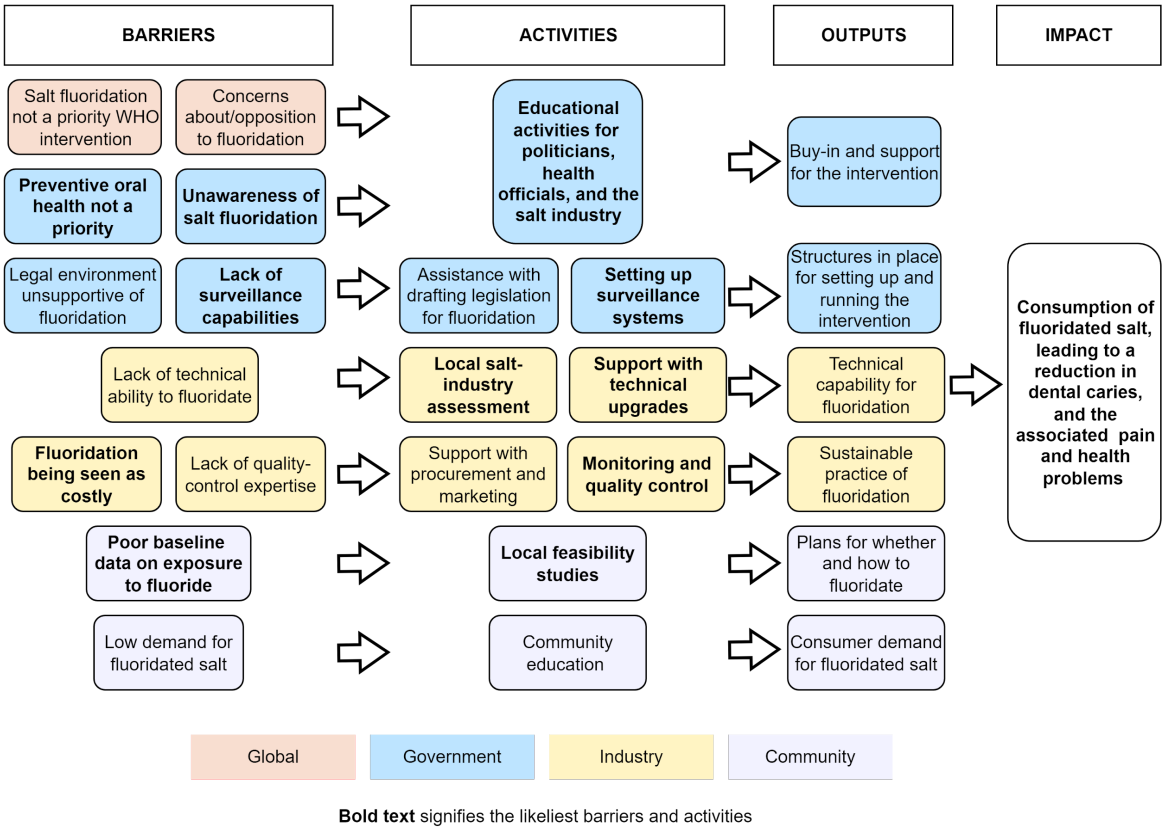

Figure 2: Theory of change for a salt-fluoridation program (editable version)

- In order to achieve **buy-in and support for the intervention**, we assume that:
  - Our educational activities can create buy-in from policymakers and health officials
  - Our educational activities can create interest from the salt industry
- In order to **put in place structures for setting up and running the intervention**, we assume that:
  - We can effectively support the government with drafting necessary legislation
  - We can effectively set up surveillance systems for fluoride distribution that will be used by the relevant stakeholders
- In order for salt-processing plants to **have the technical capability for fluoridation**, we assume that:
  - The industry is consolidated enough and developed enough[15] for upgrades to be affordable for us

[15] An important determinant is the existence of pre-existing machinery for iodization.

- In order to achieve **a sustainable practice of salt fluoridation** at the facility level, we assume that:
  - Interest in the program from the salt industry will be sustained and long-lasting
  - The government can effectively monitor the program and enforce quality (with our support)
- In order to be able to **make good decisions about whether and where to fluoridate**, we assume that:
  - We are able to run feasibility studies (such as groundwater fluoride exposure and baseline caries prevalence) in an effective and affordable manner
- In order to **increase consumer demand for fluoridated salt**, we assume that:
  - We can do forms of advertising and/or community education in an affordable manner
  - Our educational activities are effective at changing people's knowledge and beliefs

Scale: key uncertainty, high uncertainty, some uncertainty, low uncertainty, unconcerning

4 Geographic mapping

4.1 High-level considerations

Which countries this intervention would make sense in depends on multiple factors:[16]

1) The current and projected burden of oral diseases
2) Exposure to fluoride from drinking water
3) Use of fluoride toothpaste
4) Mandatory salt fluoridation is already in place

[16] Other relevant considerations are discussed in section 3.1.

1) The current and projected burden of oral diseases

The burden of oral diseases significantly varies between different regions of the world (see Figure 3). Overall, despite their much higher investments in oral health, HICs have a higher burden than MICs and LICs. This is primarily due to their higher consumption of simple sugars, such as from sweetened beverages.

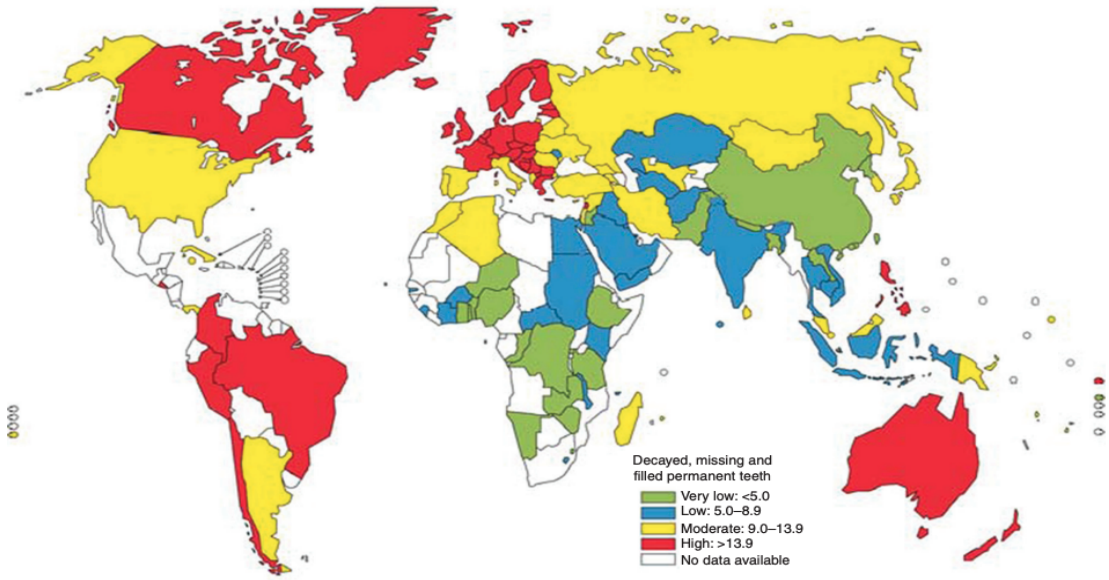

Figure 3: Dental caries level in 35- to 44-year-olds. Data from the World Oral Health Report 2003 (Petersen, 2008)

There are reasons to believe that this situation may change in the near future, as poorer countries undergo the so-called "nutrition transition" toward diets high in sugars, fat, and animal foods (Reardon et al., 2021). Supporting this concern is the fact that large players in the sweetened-beverage industry, such as Coca-Cola and PepsiCo, have been investing large sums of money for operations and marketing in LMICs (Peres et al., 2019).

Nevertheless, this situation presents a conundrum: Is it better to focus the intervention on countries with an existing high burden of oral diseases – such as many MICs in Latin America – or focus on LMICs in Sub-Saharan Africa or Asia, before their burden of oral diseases gets worse?

While arguments can be made both ways, we think that working in countries with an existing high burden of oral diseases would be more tractable, as it will be easier to demonstrate to the governments that there is a need for action. It will also be easier to demonstrate impact with studies showing a reduction in caries prevalence.

Moreover, the existing data on the burden of caries in different regions of the world do not currently show any notable regional trends (see Figure 4), so the argument that the situation is changing doesn't, as of yet, seem empirically supported. We note, however, that our interviewees have questioned the quality of the available data on the prevalence of caries, as well as how the DALY burden of caries is calculated; so we think it's plausible that the situation is evolving differently than the figure below indicates.

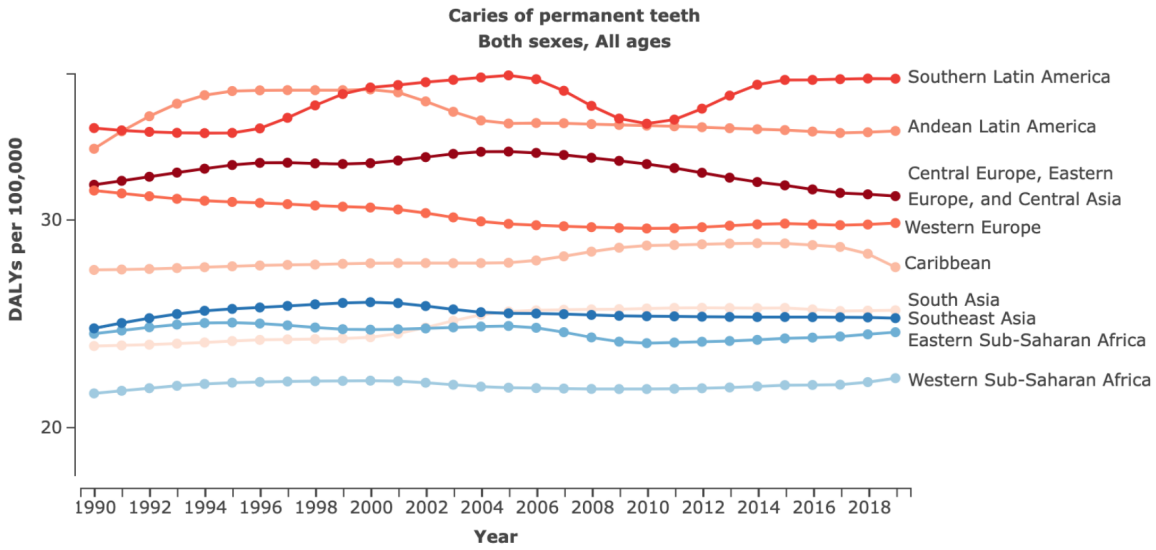

Figure 4: Sugar-sweetened beverage exposure across countries (GBD Compare | IHME Viz Hub, n.d.)

2) Exposure to fluoride from drinking water

Fluoride is naturally present in groundwater sources around the world. In most areas around the world, the levels are below the 0.7mg/l level – which is recommended for optimal caries prevention. However, some areas naturally have levels that are around this optimal point and other areas have levels exceeding 1.5mg/l – which is considered the safe upper limit. These areas are therefore receiving sufficient levels of fluoride for caries prevention, and would not benefit from a salt-fluoridation program.

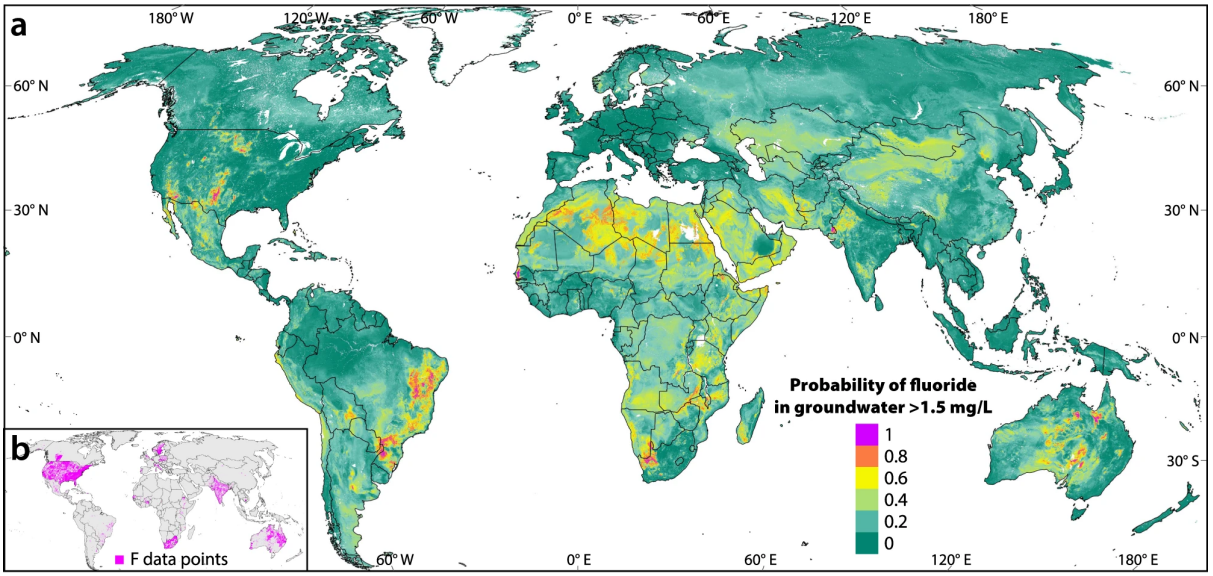

Figure 5: Estimated probability of groundwater fluoride levels exceeding the recommended safe levels (Podgorski & Berg, 2022)

Figure 5 above shows the simulated probability of groundwater fluoride levels exceeding 1.5mg/l, which is considered to be the safe upper limit (Podgorski & Berg, 2022). We can see that large parts of northern and eastern Africa are already exposed to high fluoride levels, as are some regions of northwestern India, northern and western China, and eastern and southern Brazil. In fact, many of these regions have documented problems of high exposure to fluoride, leading to endemic fluorosis (Nocella et al., 2022; Del Bello, 2022; Het et al., 2020; Cangussu et al., 2002). Note, however, that groundwater fluoride concentrations can vary greatly within one country, so salt fluoridation may make sense in some regions in these countries and not others.

Another consideration is whether countries are receiving artificially-fluoridated water. Water fluoridation programs have generally tended to be adopted by HICs in Europe and North America, since water fluoridation requires a well-functioning piped water infrastructure. In terms of LMICs, these include: Chile (around 70% of the population), Brazil (40%), Libya (6%), and Vietnam (4%) (Wikipedia, n.d.).

3) Prevalence of tooth brushing with fluoride toothpaste

Tooth brushing with fluoride toothpaste is the 'gold standard' method of preventing dental cavities. If the majority of the population of a given country regularly brush their teeth, the additional benefit of salt fluoridation is limited.

In our view, community fluoridation programs make most sense if a country or a region is currently too poor for its people to afford fluoride toothpaste, and the health system is too weak to teach tooth brushing on a large scale.

However, we have not been able to find good-quality data on the prevalence of tooth brushing by country. In fact, this data may not exist. The recently-released WHO Mid-Term Progress Report on the implementation of the 2016-2025 strategy for oral diseases in Africa noted that, while 39 member states claim that they had improved access to fluoride toothpaste and promoted its utilization, "*it is difficult to measure how these interventions have contributed to reducing common risk factors, while it is equally difficult to assess the coverage of the population using fluoride toothpaste as there are not enough resources to put appropriate surveillance systems in place.*" (WHO, 2022e)

Instead, we use two proxy variables in our geographical mapping. First, a country's general income level seems to be strongly predictive of its usage of fluoride toothpaste: According to a survey of dental officers from 101 countries, some 82% of people in HICs benefit from fluoride in toothpaste, while only 52% in MICs and 31% in LICs do (Petersen et al., 2019).

Our second proxy for the use of fluoride toothpaste is its affordability. Presumably, if fluoride toothpaste is expensive relative to people's incomes in a given country, consumption will be low. The graph below shows how much the relative price of toothpaste varies by country: In some countries, even low-paid workers can buy a year's supply of toothpaste for a few hours' wage; in other countries, they may need to work for several days to afford a year's supply.

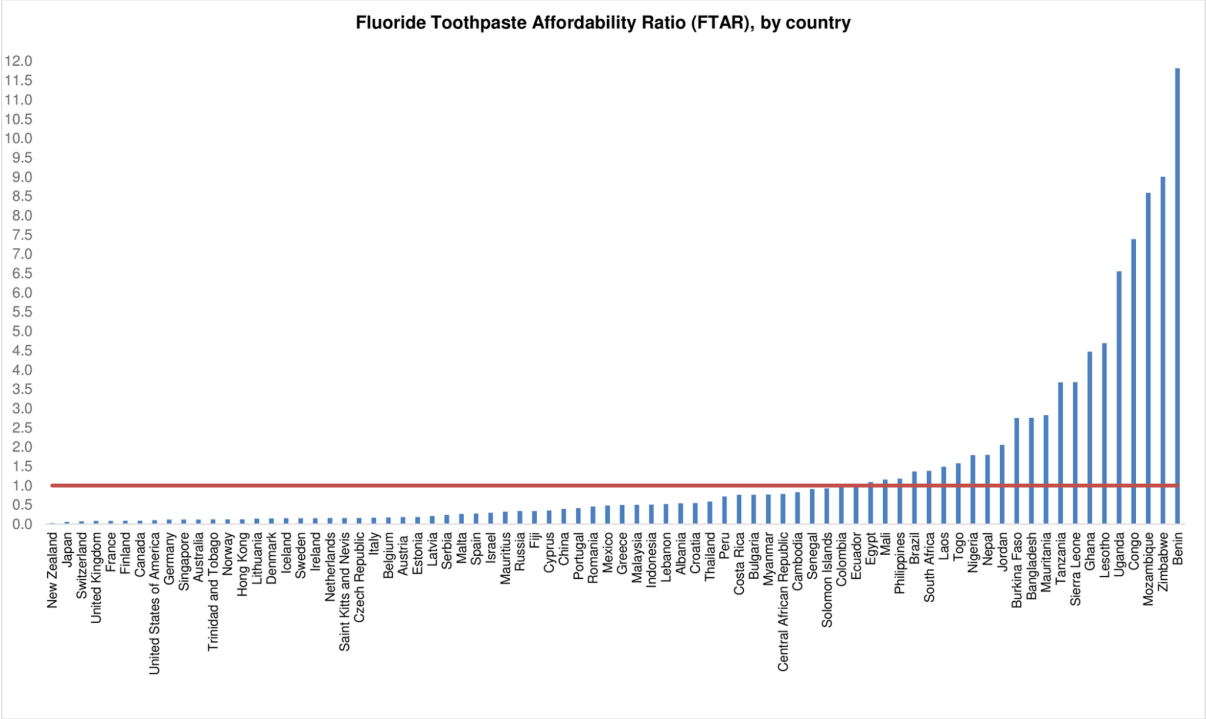

Figure 6: Affordability of fluoride toothpaste by country. A ratio above 1 indicates that toothpaste may not be affordable in that country (Gkekas et al., 2022)

4) Mandatory salt fluoridation is already in place

A few countries already have mandatory or voluntary salt-fluoridation policies. We outline these countries, by region, in this section. We would deprioritize working in countries that already have policies in place, as fluoridation is likely to be less neglected there. However, it may also be the case that working in countries with existing policies around salt fluoridation could be especially impactful: While these countries have preexisting buy-in and commitment to fluoridation, many of them are struggling with scaling up their programs and keeping them running. This is due to various operational and implementation challenges (based on our conversation with fluoridation and iodization experts). As such, the support of a small charity could translate into a large shift in the scale of their programs. We expect this to vary from country to country, so it is difficult to make a generic conclusion.

Africa

- Namibia:[17] Mandatory fortification of salt with iodine and fluoride
- Madagascar: Mandatory fortification of salt with iodine and fluoride[18]

[17] All data taken from the Global Fortification Data Exchange
[18] In reality, only around 20% of salt is fluoridated (based on our expert interviews)

According to the World Health Organization, Ethiopia, Eswatini, and The Gambia also reported promoting salt fluoridation (WHO, 2022e). It is not clear under what capacity this promotion took place.

Americas

- Mexico: Mandatory fortification of salt with iodine and fluoride
- Guatemala: Mandatory fortification of salt with iodine and fluoride
- Nicaragua: Mandatory fortification of salt with iodine and fluoride
- Costa Rica: Mandatory fortification of salt with iodine and fluoride
- Dominican Republic: Mandatory fortification of salt with iodine and fluoride
- Venezuela: Mandatory fortification of salt with iodine and fluoride
- Colombia: Mandatory fortification of salt with iodine and fluoride
- Ecuador: Mandatory fortification of salt with iodine and fluoride
- Peru: Mandatory fortification of salt with iodine and fluoride

Marthaler et al. (2011) also note that fluoridated salt is available in Belize, Bolivia, Uruguay, Cuba, and Jamaica, likely through voluntary fortification standards.

Asia

Currently, no countries in Asia have a mandatory or voluntary salt-fluoridation policy, according to the Global Fortification Data Exchange.

Europe

- Slovakia: Mandatory fortification of salt with iodine and fluoride

Marthaler et al. (2011) also note that fluoridated salt is available in Switzerland, Spain, France, Germany, Austria, Czech Republic, Greece, and the Netherlands, likely through voluntary fortification standards.

Oceania

Currently, no countries in Oceania have a mandatory or voluntary salt-fluoridation policy.

4.2 Where existing organizations work

To our knowledge, there are no global organizations dedicated to implementing or scaling salt fluoridation. However, national governments of some countries cooperate on implementing fluoridation programs. Most notable, the PAHO, a UN agency, has worked on promoting salt fluoridation in the Americas region since

1962. As a result of its work, there are currently national programs for caries prevention via salt fluoridation in the majority of Central and South American countries (Estupiñán-Day, 2005).

The WHO Africa office monitors which countries promote salt fluoridation but, to our knowledge, doesn't actively support countries in such programs.

4.3 Geographic assessment

In our geographic assessment, we built a weighted-factor model that takes into consideration the above factors. Namely, we construct:

- A **scale** score, based on the number of DALYs lost due to caries of permanent teeth (based on the Global Burden of Disease dataset, 2019)
- A score of **suitability for salt iodization**, based on a combination of (a) groundwater (or piped water) fluoride levels,[19] (b) having a mandatory policy on salt iodization,[20] (c) having an existing policy on salt fluoridation, (d) toothpaste affordability, (e) estimated use of fluoride toothpaste based on the country income level,[21] and (f) the density of dentists in the country.
- A **general tractability index**, made up of a combination of the Fragile State Index, the Corruption Perception Index, and the Rule of Law Index.

Ideally, we would also integrate other information, such as the percentage of salt that is already fluoridated, the number and size of salt processing facilities, and whether much salt is imported or exported. However, we weren't able to find or collate the necessary information.

Based on our model, out of the 15 highest-ranking countries, all but two (Nepal and Sri Lanka) are in Sub-Saharan Africa. The majority are in West Africa, reflecting our understanding that groundwater fluoride levels are generally low there.

Rank	Country	Region	Total score
1	Burkina Faso	Sub-Saharan Africa	1.39
2	Guinea-Bissau	Sub-Saharan Africa	1.35
3	Togo	Sub-Saharan Africa	1.35

[19] Note that this is based on a quick reading of the data in Figure 5; a more detailed examination may alter our ratings. Additionally, groundwater fluoride levels may vary significantly within a country, with some regions having very low levels and some having excessive levels. High within-country variation may itself be a barrier to salt fluoridation, as it would require very careful control of where fluoridated salt is and isn't made available.
[20] If salt iodization is done and enforced, adding fluoridation on top should be easier.
[21] Based on Petersen et al. (2019), a country's income level (low/medium/high) is a strong predictor of its average use of fluoride toothpaste.

4	Liberia	Sub-Saharan Africa	1.32
5	Cabo Verde	Sub-Saharan Africa	1.21
6	Guinea	Sub-Saharan Africa	1.19
7	Benin	Sub-Saharan Africa	1.18
8	Sao Tome and Principe	Sub-Saharan Africa	1.06
9	Ghana	Sub-Saharan Africa	1.05
10	Lesotho	Sub-Saharan Africa	0.99
11	Gambia	Sub-Saharan Africa	0.94
12	Côte d'Ivoire	Sub-Saharan Africa	0.87
13	Nepal	South Asia	0.86
14	Sri Lanka	South Asia	0.80
15	Eswatini	Sub-Saharan Africa	0.79

5 Quality of evidence

5.1 Evidence that the change has the expected health effects

The evidence that salt fluoridation leads to a reduction in tooth decay is strong. While no RCTs have been run, there are several community trials (essentially comparisons between small numbers of selected intervention and control areas) and many countries or areas with pre/post comparisons. While this type of evidence wouldn't normally be perceived as strong, we believe that it is justified, given the effect sizes observed.

The extent of tooth decay is normally measured by the number of decayed, missing or filled teeth (DMFT). This value ranges from 0 to 20 for deciduous teeth, and from 0 to 32 for permanent teeth.

Below is a selection of studies on the effects of salt fluoridation on the DMFT score:

- **A community trial in Hungary** in the years 1966-1976, where fluoridated salt was introduced to some villages but not others, found reductions in DMFT (reported in Estupiñán-Day (2005), pp 7-9) of around 60% for children aged 2-6 and around 40% in children aged 12-14.

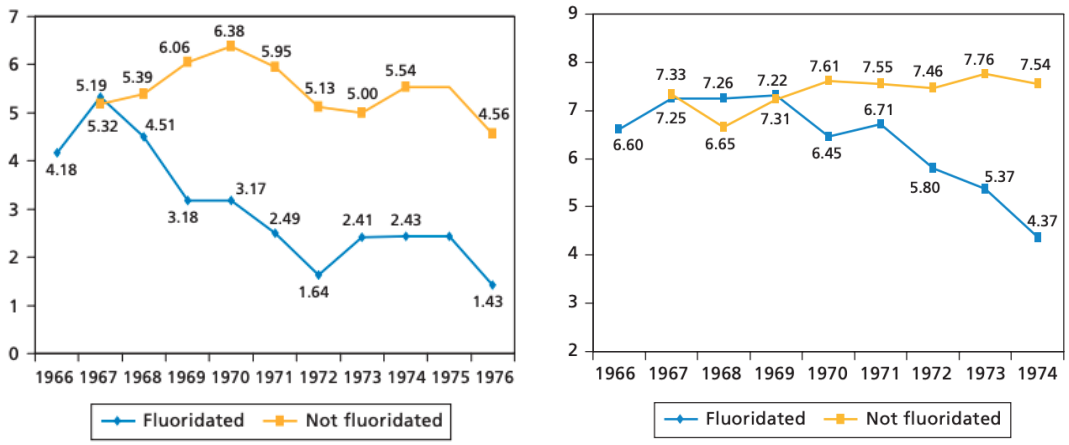

Figure 7: DMFT trends in one community with fluoridated salt vs. two communities without, in Hungary, 1966-1976. Left: ages 2-6; right: ages 12-14 (Estupiñán-Day, 2005)

- **A community trial in Colombia** in the years 1964–1972 found a reduction in DMFT scores of around 55%

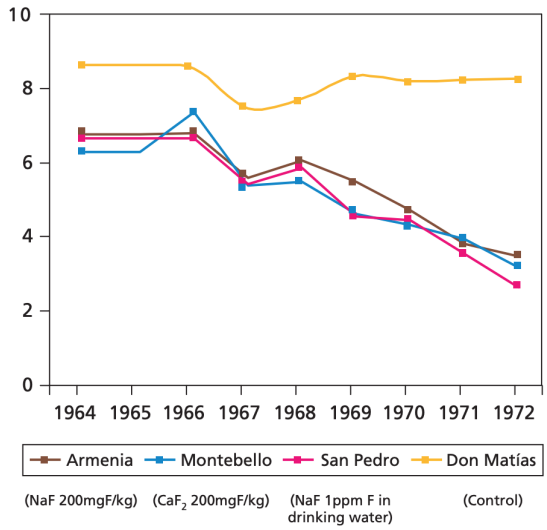

Figure 8: DMFT trends in three communities with fluoridated salt vs. one community without, in Colombia, 1964-1972. ages 6-14 (Estupiñán-Day, 2005)

- **Costa Rica**, which introduced a nationwide salt-fluoridation program in 1987, saw its average DMFT in 12-year-olds decrease by 42%, from 8.4 in 1988 to 4.9 in 1992.

- **Jamaica** introduced a nationwide salt fluoridation trial in 1987. The average DMFT in children of 12 years of age decreased from 6.7 in 1984 to 1.1 in 1995, a reduction of 84%.

Note that the latter two examples are observational studies, and the periods covered coincided with rising use of fluoride toothpaste, so it's difficult to say what proportion of the reduction was attributable to the fluoridation programs (Pollick, 2013).

Yengopal et al. (2010) performed a meta-analysis of eight studies from Europe and South America. They found the following effects:

- For 6-8-year-olds: a reduction in DMFT of 0.98
- For 9-12-year-olds: a reduction in DMFT of 2.13
- For 13-15-year-olds: a reduction in DMFT of 4.22.

In all three categories, those effects translated into roughly 50% relative reductions.

The one concern we have about the above studies, is that all of them were performed in the 1970s to 1990s in countries with a high sugar consumption and very high baseline levels of caries. For instance, the control groups in the 13-15-year-old age categories in the studies had average DMFT scores of between 6 and 9 – something that's rarely seen anywhere in the world nowadays. As such, we think it's plausible that relative effect sizes today would be smaller than those observed in the reported studies. One reassuring observation, though, is that the effect sizes for 6-8-year-olds, who only had baseline DMFT scores of between 1.2 and 1.7, were still around 50% in relative terms, consistent with the other age groups. However, even with an effect size of 25% (as assumed in our CEA in section 7), we still think that this would be a very effective, and cost-effective, intervention.

5.2 Evidence that a charity can make change in this space

To our knowledge, no small charity has previously worked on salt fluoridation; the past programs that we are aware of were usually done with the support of the WHO. While this is somewhat concerning, we do not have any specific reasons to think a charity could *not* do this work. Based on our expert interviews, we believe that a new charity, possibly with the backing of a university, could feasibly and effectively implement this intervention.

6 Expert views

6.1 Sante Leandro Baldi (Università degli Studi di Milano)

Profile: A researcher at Università degli Studi di Milano, focused on global oral health, epidemiology and prevention of non-communicable diseases, and the social determinants of health and health inequalities.

Main takeaways: Mr. Baldi confirmed to us that oral health is a globally neglected issue. It is often seen as a private issue, and a problem that sits with dentists rather than public health officials – but dentists are usually privately employed, so don't always have the incentive to focus on prevention.

In terms of interventions, water and salt fluoridation are the most cost-effective solutions but will not be the most feasible everywhere, as there is a need for political top-down support. Different countries may also have different levels of cultural opposition to fluoridation.

He suggested that we consider focusing on expanding access to affordable toothpaste. One option may be to support local communities in making their own fluoride toothpaste, such as by offering loans or grants to local entrepreneurs to start local production.

Based on his experience from Tanzania, he didn't think that teaching people to brush their teeth with toothpaste would be difficult – people with dental problems are keen to learn and improve their oral health. There are also many forms of education touchpoints to consider: school, primary care, antenatal care, via religious centers, via WhatsApp, etc.

6.2 Prof. Howard Pollick (University of California, San Francisco)

Profile: Professor of preventive and restorative dental sciences at UC San Francisco School of Dentistry; fluoridation consultant at the California Department of Public Health, Office of Oral Health.

Main takeaways: Professor Pollick was supportive of the idea of salt fluoridation, saying it has strong evidence behind it and is feasible in places where water fluoridation isn't. However, he pointed out several concerns:

- The rising adoption of fluoride toothpaste has reduced the ability for fluoridation to have a demonstrable effect.
- It is important to get community buy-in for any kind of fluoridation program (Prof. Pollick and his colleagues wrote a manual on fluoridation and how to go about convincing communities that they should support it). It's important to find communities where oral diseases are rampant.
- It is also important to get political support and to, as an organization, provide support for politicians so that they can point to us as the experts in case there is disagreement about whether or not to fluoridate.
- There may be resistance from authorities to the program because dental problems aren't seen as significant, but salt consumption – which contributes to hypertension – is. This was less of an issue in the 60s and 70s, because the link with hypertension wasn't as clear.

He warned that it would likely be a multi-year process to set up a program.

6.3 Expert C

Main takeaways: Our interviewee was very supportive of additional resources being directed toward salt fluoridation, which has historically been a lower-priority intervention than other kinds of fluoride exposure. The WHO recommends water fluoridation – even though it's not feasible in many places – and brushing with toothpaste, even though it often costs $10 per person per year (as opposed to a few cents with salt fluoridation).

They encouraged us to consider working in Latin America where there are still a lot of problems with oral health. The program by PAHO was shut down, and since then there's been little coordination and oversight. Many programs have suffered serious setbacks as there is now no-one to assist countries when they need support to manage and monitor their programs. Our organization could pick up where others left off.

They have less experience with Sub-Saharan Africa. However, they pointed out that salt production there is more artisanal and less industrial than in Latin America (where around 40% is owned by a single company), so it may be more difficult to do work there. They also pointed out that many African countries follow WHO

recommendations very closely, which may make it difficult to argue for salt fluoridation there. They recommended that we connect with WHO's regional office in Africa to understand their strategy. They pointed out that fluoridation strategies need to be locally tailored, so fluoridation experience from South America or toothpaste experience from Asia may not be applicable in Africa.

In terms of potential work in Latin America, they said that we would need to start with some feasibility studies, such as an assessment of the actual state of salt fluoridation in the region, studying the distribution systems, the supply chains, etc.

6.4 Dr. Werner Schultink (Iodine Global Network)

Profile: Executive Director of the Iodine Global Network; with a background in nutrition, epidemiology and public health research, Dr. Schultink provides guidance and leadership on strategic iodization program implementation and capacity building for countries in Asia, Africa, Latin America and Eastern Europe.

Main takeaways: Dr. Schultink confirmed to us that the activities we listed in our ToC are the right ones. That is, there is a need for baseline feasibility studies, for technical assistance to salt plants, support with monitoring, and educational activities. Education is primarily important for policymakers and health workers, so that they are on board with and supportive of the program. Education for the general public may be beneficial, but likely not crucial – plus it is expensive and hard to do.

Dr. Schultink also told us that there are concerns about fortification programs' sustainability. Even in the iodization space, which has extensive international support and a strong history, many countries' programs are sliding back because of insufficient support from governments and NGOs. Even though fortification isn't very costly once set up, it is still a non-negligible expense for the salt companies, which they may not be willing to cover themselves. And it has been difficult recently to attract sufficient international funding, since the major funders (like UNICEF) have now ended much of their support.

Another challenge is that the salt industry in many countries, such as Pakistan or Bangladesh, is very disjointed, with a very large number of small producers. This varies a lot, though.

Because of these concerns, Dr. Schultink thought that the chance of a success of a new small charity in this space is limited.

6.5 Shakun Sharma (Fortify Health)

Profile: Director of Programs at Fortify Health, previously a Project Manager in the Large-Scale Food Fortification Program at the Global Alliance for Improved Nutrition (GAIN).

Main takeaways: Ms. Sharma agreed that it was a good idea to focus on exposure to fluoride as an intervention, since oral health in LMICs is very much neglected. In many parts of India, for example, people brush their teeth with teeth-cleaning twigs, without the use of fluoride toothpaste. Oral health is also not something that's often discussed at the policy level.

In terms of the charity's activities, she recommended that early engagement with the industry is important, to understand their views and their receptiveness. Focus should be on the big players, as the smaller ones will often follow suit once an example has been set.. . She recommended focusing on enabling access to fortified staple(s) by working with open market players, which in turn might inform the government to make decisions on mandatory fortification. In terms of monitoring and compliance, while this is something that a charity can help with, the mandate ultimately sits with the government. They are the ones who set the fortification standards, and can ensure the compliance to those standards by producers (even if those standards are voluntary).

7 Cost-effectiveness

We have modeled the cost-effectiveness of running a salt-fluoridation program in Togo. Togo was chosen because (a) it ranked highly in our geographic assessment, (b) it is a coastal country, therefore presumably with an existing salt industry, (c) the cost-effectiveness in Togo should be roughly representative of other countries in the region. We note, however, that this choice is quite poorly informed: Due to us not having good data on the salt industries of different countries – such as how much salt they produce, how much they import and export, and how many salt-processing plants there are – it may be the case that Togo, specifically, is a country where this intervention would not make sense.

Our model makes the following assumptions:

- The costs for the charity would consist of: (i) charity personnel costs, (ii) the costs of feasibility studies, including groundwater fluoride measurement and a baseline caries assessment, (iii) the cost of chemicals for fluoridation, (iv) a budget for training staff of salt plants, plus making minor technical upgrades, (v) cost of one staff embedded in the government. While some of these costs are estimated quite accurately (i, iii, and v) based on past data, some (ii and iv) are rather poorly informed guesses and may be quite inaccurate.
- To estimate the number of people who could benefit from the intervention, we multiplied Togo's population by the prevalence of untreated caries, the percentage consuming iodized salt, a multiplier to account for potential program reach (estimated at 75%), and a downward adjustment for the proportion of the population already benefiting from fluoride due to using toothpaste.
- We estimated the effect of the intervention in five different ways:
    I. Looking only at the effects of pain, using the DALY disability weight for dental pain from the GBD study (i.e. 0.01)
    II. Looking only at the effects of pain, but using our own adjusted DALY disability weights (i.e., 0.05)[22]

[22] We suspect that GBD disability weights may underestimate the severity of dental pain. Our adjusted estimate is based on an analogy with lower back pain, which has weights 0.02, 0.054, and 0.272 for mild, moderate, and severe pain. Assuming that the ratios (0.054/0.02 and 0.272/0.054) for dental pain are the same, and that mild dental pain has a weight of 0.01, we get 0.027 for moderate dental pain and 0.136 for severe dental pain. Then, we estimate that the prevalence of mild/moderate/severe dental pain is 25%/50%/25% (based on Kakoei et al. 2013 and made slightly more conservative) and get 25%*0.01 + 50%*0.027 + 25%*0.136 = 0.05.

III. Looking at the effects of pain and other potential health effects of preventing tooth decay, reducing the risk of cardiovascular disease and diabetes[23]
IV. Same as III but using our adjusted DALY disability weights
V. Looking at the effects of pain using WELLBYs

- While the average reduction in caries observed in the meta-analysis by Yengopal et al. (2010) was around 50%, we reduce this to 33%, as effects may now be lower due to the generally lower baseline level of caries (Sampaio & Levy, 2011).

For the five models listed above, we get the following results:

I.	Pain only, original DALY disability weights	$179.21/DALY
II.	Pain only, adjusted DALY disability weights	$35.84/DALY
III.	Including other health effects, original DALY weights	$110.19/DALY
IV.	Including other health effects, adjusted DALY weights	$31.85/DALY
V.	Well-being effects of pain	$10.24/WELLBY

Assuming that our bar is around $100/DALY, this makes the intervention cost-effective under some assumptions, but not under others.

However, please see section 8.8.1 where we additionally model the potential negative health effects of fluoride exposure.

Note that if our well-being analysis is correct, it would put this intervention on par with the cost-effectiveness of StrongMinds (a mental health charity in Africa), according to an analysis by the Happier Lives Institute (Plant, 2022).

8 Implementation

This section summarizes our concerns (or lack thereof) about different aspects of a new charity putting this idea into practice.

[23] Whether or not the relationship between tooth decay and cardiovascular disease/diabetes is causal is uncertain, so we discount the effects by 60% and 50%, following Bettle (2022).

Factor	How concerning this is
Talent (difficulty of finding founders and/or key hires)	Low
Access to information	High
Access to relevant stakeholders	Low-Medium
Feedback loops	Medium
Funding	Medium-high
Scale of the problem	Low
Neglectedness	Low
Execution difficulty/Tractability	Low-medium
Negative externalities	Medium
Positive externalities	Low-medium

8.1 Talent

While it may be beneficial to have someone with a medical or engineering background in the core team, we think that neither of these are necessary. The fact that salt fortification has been implemented in different parts of the world in the past provides a blueprint for how to go about it, which a capable generalist should be able to follow. In a conversation about the policy aspects of food fortification, Anne Wanlund (Canopie, previously Project Health Children) told us "[once you have a blueprint], then anybody who has grit and wants to see a big change in government and can develop good relationships with ministries and other stakeholders could do the job." In terms of the industry-focused part of the charity's work, we can look at the experience of Fortify Health who have successfully been working with millers on implementing wheat-fortification technology, without a specialist technical background.

8.2 Access to information

Work on oral health has been globally neglected for the past two-three decades, so baseline data on many relevant variables – such as the state of oral health in different regions, groundwater fluoride levels or the use of fluoride toothpaste – is often either missing or out of date. As such, the charity's early progress may be hampered by the need to identify suitable data sources, or to run local feasibility studies and collect primary data.

8.3 Access to stakeholders

We are uncertain about how difficult it will be to access the relevant stakeholders for this intervention, and this may vary by region.

Access to stakeholders in Africa may be difficult due to their reliance on the WHO which doesn't currently recommend salt fluoridation.

Access to stakeholders in Latin America would be relatively simple, as we have contacts in the region who could connect us with the relevant stakeholders.

8.4 Feedback loops

It should be relatively easy to run small-scale studies to obtain data on how the intervention is progressing from the sales of fluoridated salt and monitoring activities looking at fluoride concentrations. However, collecting evidence on the actual health impacts of fluoridation is difficult, with effects taking about seven years to be observable (Estupiñán-Day, 2005). Moreover, it will be extremely difficult to run RCTs in this space (to our knowledge, no past authors have), so any impact evaluations will need to rely on comparisons between target and non-target communities. As such, feedback loops are expected to be longer and less robust than for many other global health interventions.

8.5 Funding

The difficulty of securing funding in this space is quite uncertain. Oral health has been very neglected in the past two decades, with limited funding going into preventive programs. While there now seems to be renewed interest with the new WHO oral health strategy, salt fluoridation isn't high on the agenda so it may not be easy to attract money from major international funders (WHO, 2022d).

The traditional funders of international food fortification may also not be interested in fluoridation, since fluoride doesn't rank highly in terms of "public health significance" (WHO, 2006). This is likely due to its negligible impact on mortality.

That being said, there *are* funders interested in global oral health. The Borrow Foundation has historically funded various projects in this space (including helping fund the Lancet Commission on Oral Health), and Founders Pledge is currently looking for charities to fund in the space of preventive oral health.

It may be worth investigating why GiveWell, who previously used to recommend multiple "standout charities" in the micronutrient fortification space (Food Fortification Initiative, GAIN's salt iodization program, Iodine Global Network, Sanku/Project Healthy Children), has discontinued recommending these charities. To our understanding, the argument was based on their modeled cost-effectiveness.[24] GAIN and the Iodine Global Network *are* rated as high-impact funding opportunities by Founders Pledge.

8.6 Scale of the problem

While poor oral health seems like a large and neglected problem, it is somewhat difficult to assess this accurately, given the lack of good data on the issue. Small-scale studies and anecdotal information suggests that bad oral health causes a lot of preventable suffering, especially in LMICs with poor access to restorative care. However, available data (such as from the Global Burden of Disease study) also show that oral health in LMICs has been comparatively good, owing largely to their low-sugar diets and, in some cases, exposure to sufficient levels of fluoride in groundwater. There is a big concern about oral health worsening with shifting diets – but that's a projection rather than the current reality.

8.7 Execution difficulty and tractability

Salt fortification, including fluoridation, is something that has previously been done in multiple countries around the world, so we are confident that this issue is tractable. However, each country has its own unique challenges that will need to be overcome. Additionally, all of the past programs we are aware of were either led by the government or by a large international organization (such as the WHO). As such, we have some uncertainties about the ability of a small new charity to effect change.

8.8 Negative externalities

While exposure to "optimal" levels of fluoride decreases the risk of tooth decay, exposure to high levels of fluoride can lead to a range of negative health effects. The most common are changes to the tooth enamel known as fluorosis. These typically take the form of harmless cosmetic changes to the teeth, in the form of discoloration or lacy white markings. In the UK, between one and two thirds of teenagers have detectable signs of fluorosis (Morris et al., 2022).

[24] Though there have been anecdotal concerns that GiveWell's models undervalue policy interventions compared to community interventions.

Fluoridation interventions themselves have been shown to be associated with the risk of fluorosis, including the consumption fluoridated water, fluoridated salt, and fluoride toothpaste (U.S. Department of Health and Human Services, 2015; Vallejos-Sánchez et al., 2009). However, the prevalence of fluorosis is actually associated with a lower risk of caries, so it is unclear to what extent fluorosis should actually be seen as problematic (Iida and Kumar, 2009).

The consistent exposure to fluoride levels above the recommended upper limit of 1.5g/ml can, however, lead to range of more serious health effects, including severe dental fluorosis – which causes weak, pitted teeth – and skeletal fluorosis – which leads to bone deformities, joint stiffness, and pain while moving (ScienceDirect, n.d.; Onipe et al., 2020). Some studies suggest that fluoride may interfere with the function of the endocrine system, leading to disrupted puberty and lower fertility (Skórka-Majewicz et al., 2020).

8.8.1 Fluoride as a potential developmental neurotoxicant

Arguably the greatest concern associated with the consumption of fluoride is its potential neurotoxicity. Whether or not fluoride is harmful to brain development – especially at the low levels recommended for caries prevention – has been the subject of a debate for at least three decades. On the one hand, researchers, public interest groups, and toxicology bodies have been raising the alarm about the potential negative IQ (and other cognitive) effects of maternal and childhood fluoride exposure (Grandjean, 2019; Connett, 2012; National Toxicology Program, 2019). On the other hand, multiple public health authorities (including the UK and New Zealand public health bodies, the US Centres for Disease Control and Prevention, and the American Academy of Nutrition and Dietetics) maintain that fluoride is a safe substance at the levels recommended for fluoridation (Public Health England, 2018; Gluckmann and Skegg, 2014; Hannah and Espinoza, 2021; Palmer and Gilbert, 2012). Each side has accused the other of misinterpreting the evidence and unfairly dismissing the other side's views, making it very difficult to reach a considered, informed conclusion (Armfield, 2007; Till and Green, 2020).

In our assessment, the challenges in this area of research are that:

- Most existing studies are cross-sectional, with poor designs and small sample sizes, and therefore providing only weak evidence in support of a link between fluoride and IQ

- Most studies have been done on people exposed to high levels of fluoride, often several times above the recommended fluoridation level.[25]
- If the effects are real, they are likely on the order of 1 IQ point (see below), or 0.067 standard deviations, making them exceptionally difficult to observe.
- Some researchers have interpreted the absence of high-quality evidence of the link between low-level fluoride exposure and IQ as essentially evidence of absence (*"Expert panels [...] have not found convincing scientific evidence linking community water fluoridation with any potential adverse health effect or systemic disorder such as [...] low intelligence."*, Hannah and Espinoza, 2021) while others have interpreted it as a cause for concern (*"There has never been a single randomized controlled trial to demonstrate fluoridation's effectiveness or safety."*, Connett, 2012).

The evidence linking fluoride exposure to lower IQ comes primarily from observational studies from areas with high groundwater fluoride levels, such as China or India. A meta-analysis by Duan et al. (2018) identified 26 such studies. Of them, all showed a negative association between fluoride and IQ, with 19 effects being statistically significant. "High exposure" to fluoride (which ranged from 0.8 to 11 mg/l, with a median of 3.1 mg/l) was associated with 7.8-point lower IQ scores than "low exposure" (which ranged from 0.3 to 1.0, with a median of 0.5).[26] Many of these studies have been criticized on methodological grounds, e.g., for how they measured fluoride exposure or for not controlling for other relevant factors (such as lead exposure), so they carry the risk of various statistical biases. However, we think that they carry a relatively low risk of publication bias, judging from the shape of the funnel plot presented in the meta-analysis (Duan et al., 2018, figure 5).

[25] Though as discussed later in this section, the results are consistent with recent studies that looked directly at the effects of low-level exposure.
[26] Note that the WHO-recommended upper limit is 1.5 mg/l.

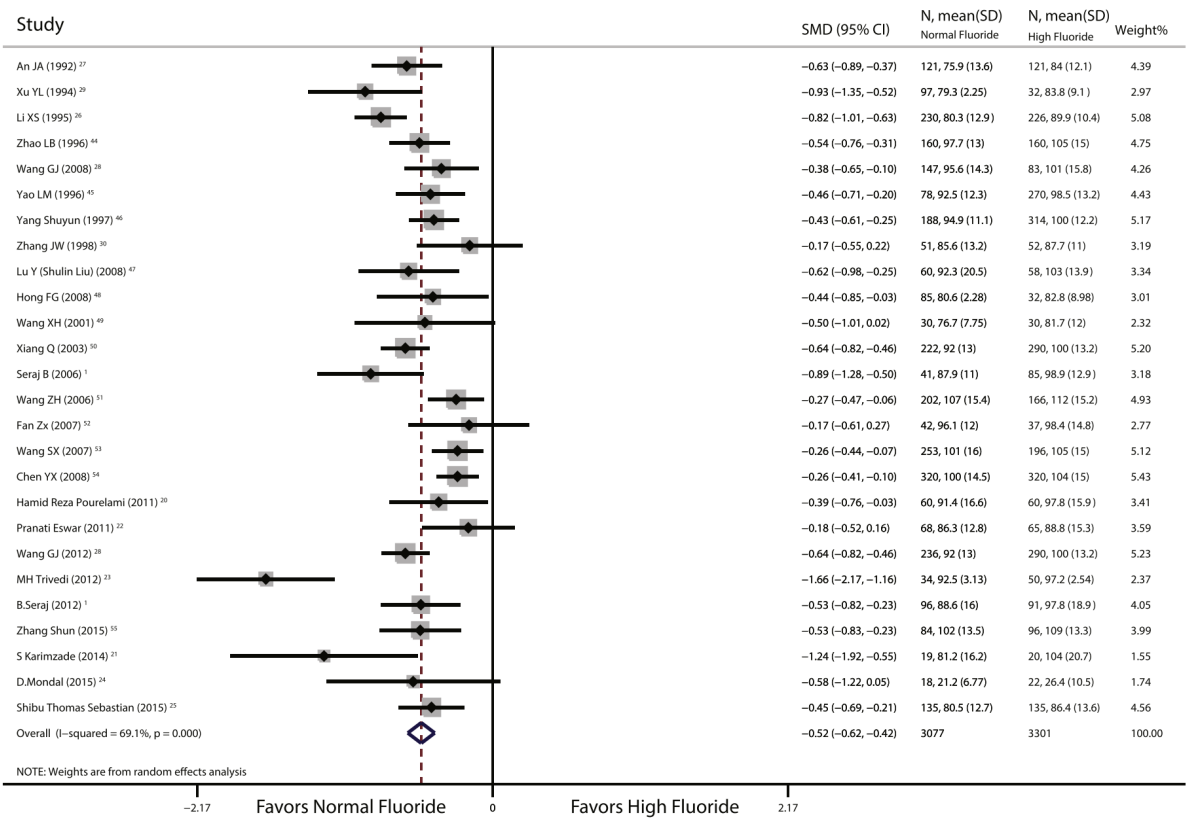

Figure 9: A forest plot on the association between fluoride and IQ (Duan et al.,2018)

The question is whether these high-exposure studies bear any relevance to the effects of exposure to low levels of fluoride. Note that when we say "low levels", we mean the recommended levels of fluoride for water fluoridation (i.e., 0.7-1 mg/l) or the equivalent amount consumed via fluoridated salt (that we estimate to be around 2 mg/day). In the absence of good-quality data, we need to rely on theory. To our understanding, there are two possibilities for the shape of the relationship between fluoride intake and IQ at levels between 0 and 1.5 mg/l (assuming that the relationship at higher levels is true):

(a) Fluoride may be safe at those levels, and only starts being harmful at higher levels. This would be similar to the case for some vitamins (mainly A and D) and some essential minerals (such as iron or calcium).

(b) Fluoride may be harmful at any level, with the negative effects having either a linear, sublinear, or superlinear relationship with IQ, starting at 0 mg/l. This would be similar to the case of heavy metals, such as lead or mercury.

To our knowledge, this point has not been settled in the literature. However, we think it is important to consider that fluoride is not an essential mineral – our body does not need it to perform any of its physiological functions (Sampaio & Levy, 2011). Its only proven beneficial effect is via topical contact with teeth where it

undergoes a chemical reaction with the enamel, thereby strengthening it (as described in section 2.3.2). Therefore, we think it is *plausible* that fluoride falls into category (b) and that its harmful effects start at zero exposure. This view is consistent with the conclusion of Spînu et al. (2022), whose modeling study indicates that sodium fluoride (the most common compound used in fluoridation) has a "medium" probability of being a developmental neurotoxicant.

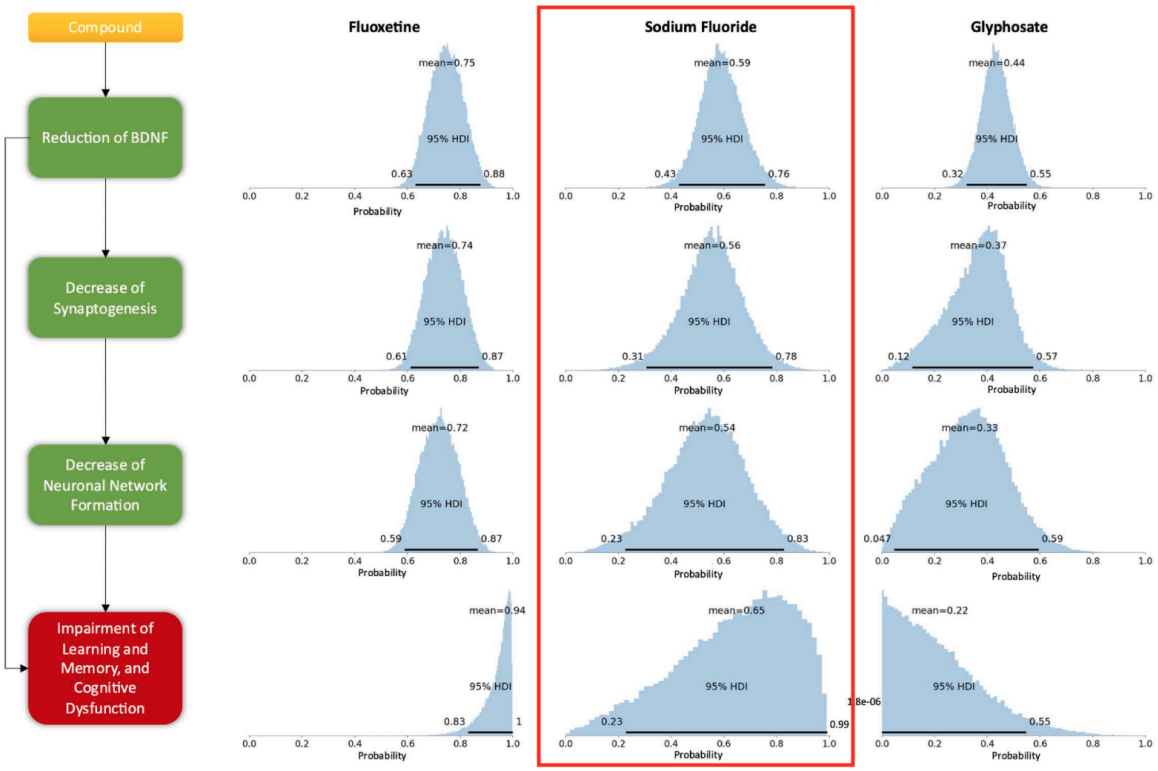

Figure 10: Modeled posterior probabilities of sodium fluoride exposure causing a reduction in the brain derived neurotrophic factor (BDNF), synaptogenesis, and neuronal network formation, and the overall probability of it impairing learning, memory and cognitive function. Fluoxetine (a high-probability neurotoxicant) and glyphosate (a low-probability neurotoxicant) are shown for comparison. Spînu et al. (2022).

In order to understand how harmful fluoride exposure at low levels could be (under the assumption that it is actually neurotoxic), we decided to expand our cost-effectiveness analysis to model these effects, with the intention of capturing the worst-case (but still reasonable scenario). Specifically, we assumed that the effect reported by Duan et al. (2018) linearly interpolates down to zero, which would imply an IQ reduction of 2.3 points for an increase of 0.7 mg/l of fluoride.[27]

[27] We discounted this effect by 20% to try to account for publication bias.

To obtain an independent estimate, we also combined this figure with the estimate obtained by Grandjean et al. (2022) in their reanalysis of two recent prospective cohort studies that looked at the relationship between fluoride and IQ at levels below 1.5 mg/l (Bashash et al., 2017; Green et al., 2019). Using a linear model to fit the data, they estimated that a 0.7 mg/l increase in fluoride results in 2.1 IQ-points loss – very consistent with the other estimate.

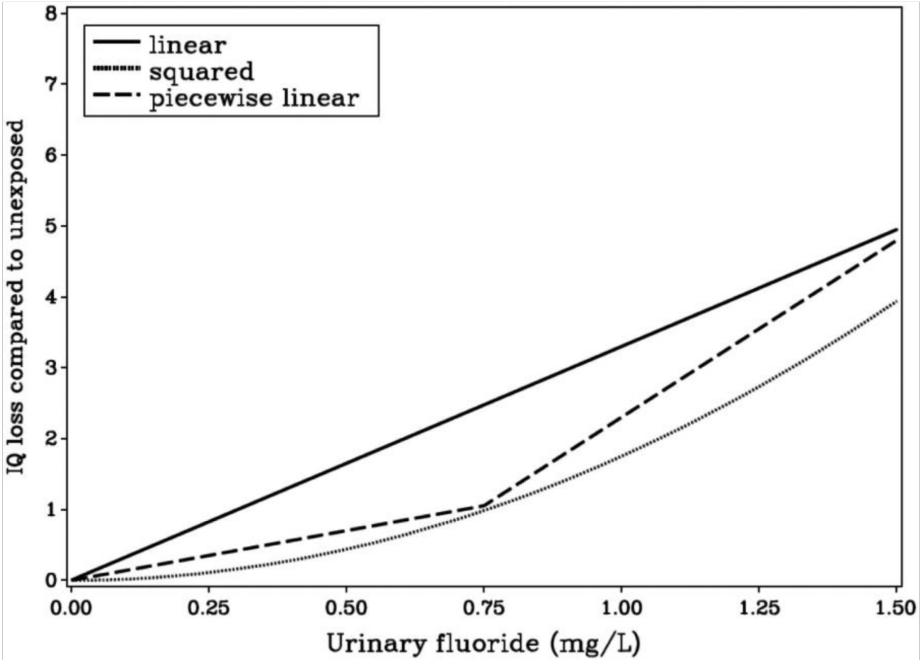

Figure 11: Association between fluoride and IQ loss, as estimated by Grandjean et al. (2022)

Lastly, for the purposes of cost-effectiveness modeling, we assumed that a reduction in IQ would result in, on average, lower wages and lower consumption in adulthood. We used GiveWell's estimate that a one-point reduction in IQ is associated with a 0.67% reduction in wages and consumption (GiveWell, n.d.), and then used their moral weights to "translate" consumption reduction into a DALY value (namely that 1 DALY equals 2.8 years of doubled income; GiveWell, 2019). We didn't model any other effects of IQ reduction than this effect on consumption, so this is likely to be an underestimate of the overall impact on people's lives.

When we plugged these numbers into our CEA, the model estimated that, in a steady-state scenario (i.e., disregarding the time delay of the IQ effect on wages), salt fluoridation in Togo may lead to a loss of 17,506 DALYs per year. This is on the same order of magnitude as our modeled positive effect by avoiding pain, 12,783 DALYs per year.

This is a very concerning result. We note that this effect-size estimate is based on low-quality observational evidence, combined with some conservative modeling assumptions. However, the fact that the negative effect of fluoridation *could* be greater than the positive intended effect means that there is a substantial *risk* of doing harm.

An additional consideration is that, given how controversial this debate is and how recent many of the studies are, we think that there are substantial risks to the tractability of work for a charity in this space. This scientific question is receiving a lot of attention at the moment, so a charity explicitly focused on fluoridation may also become the target of much scrutiny.

While we do not claim to have settled this debate, and stay open to the possibility that fluoride has no or a negligible effect on brain development at low-dose exposures, we think that the existing evidence is concerning enough for us to recommend against founding a charity in this space – at least until more conclusive research on this topic is performed.

8.9 Positive externalities

To our knowledge, there are no known positive health effects of fluoride consumption, other than its effect on the prevention of caries (which is actually due to topical exposure, rather than consumption).

However, a positive externality of running a charity focused on salt fluoridation may be its ability to diversify its portfolio and focus on the fortification of salt with other nutrients. Firstly, while the coverage of salt-iodization programs is high, many regions are at a risk of having their programs scaled down or discontinued as a result of a lack of prioritization and funding (based on our conversation with Dr. Werner Schultink). As such, a charity working on fluoridation could also provide the necessary support needed for maintaining a functional iodization program. Secondly, salt is a promising vehicle for other kinds of fortification, given its universal consumption and often relatively centralized production. Please see the Annex for a short review of other nutrients salt may be fortified with.

9 Current gaps in the research

Despite the extent of this report, there are still areas where we have uncertainties that could be resolved with further research. With more time, we would do the following:

- Get in touch with the regional offices of the WHO in Africa, Latin America, and South/Southeast Asia, to understand their views on and plans around fluoridation.
- Reach out to experts in toxicology and developmental neurotoxicants to get their view on the likelihood of fluoride being neurotoxic.
- Do more in-depth research into alternative fluoride interventions, especially into the cost and feasibility of interventions aimed at increasing the use of fluoride toothpaste.
- Connect with international experts in the field of preventive global oral health, such as Prof. Poul Erik Petersen, Prof. Stefan Listl, Prof. Richard Watt, Prof. Marco Peres, or Prof. Habib Benzian, and get their perspectives on what kind of work is most promising in this space.

It may also be the case that there are general gaps in the current state of research, and more studies are needed. As such, future cause-prioritization researchers may need to wait until more primary research is done, especially in the areas of understanding the existing burden of oral diseases in different countries and understanding whether or not fluoride acts as a developmental neurotoxicant. Both of these have received renewed interest in the recent past, so we expect there to be more clarity on these questions in the coming years.

10 Conclusion

In conclusion, our view is that while salt fluoridation is an intervention with a lot of promise, and one that may be able to cost-effectively prevent suffering on a large scale, we do not feel comfortable recommending it to charity founders at this moment, due to the concerns around the negative health effects of ingesting fluoride. If these effects are real, then there is a risk of causing a considerable amount of harm; and even if they are not, the current debate and controversy around this topic may make it difficult for a charity dedicated to fluoridation to operate and scale successfully. We recommend that future researchers revisit this topic in the future, and compare it with other preventive oral health interventions to find the safest, most effective, and most feasibly scalable way of preventing dental caries in LMICs.

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Annex: other micronutrients that could be added to salt

A1 Iron

A1.1 Precedent

In India, it is mandatory to fortify salt with both iodine and iron (Global Fortification Data Exchange, n.d.).[28] This suggests feasibility for salt fortification with iron, and this precedent could potentially be used as an argument for other countries in Asia to also fortify their salt with iron. Perhaps we could fortify salt with iodine, iron, and fluoride in Asia, and stakeholders will be more receptive as they are already used to iodine and iron fortification, and fluoridation is just an add-on.

The same is also true in Ethiopia (Global Fortification Data Exchange, n.d.), so the same arguments could be made for the feasibility and precedent of iron fortification in Africa (though we note that it is more common to find iodine and fluoride fortification standards in Africa than in Asia where we have been unable to find any; and so we might not need the addition of iron to make fluoridation acceptable, as we have argued above for in Asia).

In terms of NGOs working in this space, Nutrition International has focused on double-fortified salt (fortified with both iodine and iron) in India.

A1.2 Evidence of impact

The evidence on fortification of salt with iron and on double-fortified salt with iodine and iron is quite mixed. Evidence seems to suggest that fortification does seem to improve indicators of iron deficiency (e.g., hemoglobin concentrations and body iron stores), but the evidence that it reduces the prevalence of iron deficiency and anemia is weaker and more uncertain. Our evidence review mostly focused on a 2022 Cochrane review and studies that do not seem to be included in this review, likely because they were released after this review was completed:

- Baxter et al. (2022): This Cochrane review of 18 studies (7 RCTs, 7 cRCTs, 4 CBA studies),[29] involving over 8,800 individuals from five countries (13

[28] To our knowledge, this only affects salt used in the government safety net program, though, not salt sold on the open market.
[29] RCT = randomized controlled trial, cRCT = cluster randomized controlled trial, CBA = controlled before-after study

studies were from India), evaluating if double-fortified salt with iron and iodine is better than salt fortified with iodine alone for improving measures of iron and iodine-related nutrition found that:
  - Compared to iodized salt, double-fortified salt improves hemoglobin concentration and body iron stores slightly (*Low confidence*).
  - Double-fortified salt reduces the prevalence of anemia by 21% (*Moderate confidence*).
  - Double-fortified salt reduces urinary iodine concentration compared to iodised salt (*Low confidence*).
  - Compared to iodized salt, double-fortified salt may make little or no difference in ferritin and transferrin receptor concentration (*Low confidence*).
  - Double-fortified salt reduces the prevalence of iron deficiency anemia by 65%, compared to iodised salt (*Low confidence because of some problems with the way the studies were conducted*).
- Makkar et al. (2022): A modeling study evaluating the impact of double-fortified salt (DFS) consumption in India found that additional iron intake through DFS was predicted to reduce prevalence of iron deficiency anemia (from 10.6% to 0.7% in men and 23.8% to 20.9% in women)

A1.3 Feasibility

Studies have suggested that although it might be possible to achieve high coverage of double-fortified salt, we might still expect low adherence amongst the population. For example, Drewnowski et al. (2021) found that "Studies in controlled settings (efficacy) demonstrate that double-fortified salt reduces the prevalence of anemia and iron deficiency anemia. Studies in program settings (effectiveness) are limited and reported differing levels of DFS coverage, resulting in mixed evidence of impact on anemia." Moreover, Cyriac et al. (2020) found that although 83% of respondents had heard of DFS, and 74% had purchased it at least once, only 23% exclusively used DFS. Respondents also had low awareness about DFS benefits, and considered DFS quality as poor. This suggests that a program implementing DFS would need strong monitoring and evaluation and quality control, and may need to do some educational activities and/or demand generation work.

There are some concerns about the feasibility and affordability of double-fortified salt. The main arguments are outlined in Drewnowski et al. (2021), and are as follows: DFS production must use higher quality salt than is required for iodization alone. This ensures minimal changes in the product, specifically discoloration and

losses in iodine content. It is expected that low-resource countries with fragmented salt industries and a low proportion of industrially produced salt will find it more difficult to acquire and produce this higher quality salt. These issues seem more of a concern with ferrous sulfate, rather than encapsulated ferrous fumarate. Double-fortified salt is also more expensive to produce than iodized salt, due to higher input costs, both for input salt and the iron compound. Experience in India indicates that, on average, producing DFS costs 31–40 US dollars/metric ton or 0.03–0.04 US dollars/kg more than high-quality refined iodized salt.

Double-fortified salt is increasingly being consumed in India, through the work of the National Institute of Nutrition and Nutrition International. The National Institute of Nutrition currently reaches 60 million consumers in three Indian states (Uttar Pradesh, Madhya Pradesh, and Jharkhand).

Nutrition International developed double-fortified salt with iodine and iron (using encapsulated ferrous fumarate) more than 20 years ago, and has since had it approved for use in India in 2014. Then in 2018 the Food Safety Standards Authority of India published the standards for fortification of DFS, with minimum and maximum levels of fortification with iron and iodine. They mainly work across three different states: Tamil Nadu, Madhya Pradesh, and Gujurat.

- In Tamil Nadu they have convinced the state government to procure and use DFS in the preparation of hot cooked meals served under their school feeding program, the "Mid-Day Meal Scheme". An estimated 3.6 million schoolchildren in Tamil Nadu have benefitted from this initiative.
- In Madhya Pradesh they are supporting the state government in making DFS available through the public distribution system, to reduce the prevalence of anemia among women of reproductive age in 89 tribal blocks across 20 districts. An estimated 2.5 million women of reproductive age will benefit from this intervention.
- In Gujarat they are working to introduce DFS into Integrated Child Development Services programming across the state. This initiative is expected to benefit 3.2 million beneficiaries.

Nutrition International's policy brief outlines acceptability studies for their double-fortified salt, which have generally found good acceptability (Nutrition International, 2019).

- Based on a study by Nutrition International in 2007, 85% of consumers in Madhya Pradesh were willing to shift from regular iodized salt to EFF-DFS consumption, and were willing to pay the additional cost of INR 2 per

kilogram because of the understanding that EFF-DFS provides vital ingredients to fight diseases.

- Khanna et al. (2007) investigated the acceptability of the EFF-DFS formulation in comparison to iodized salt and other experimental formulations in a three-month household consumption study. The study reported acceptability of all salt, though iodized salt was considered the "best choice" due to its familiarity.

This policy brief also outlines how to scale up production and support governments in the promotion and scale up of this salt, based on their work in India.

A1.4 Cost-effectiveness

We couldn't find many existing cost-effectiveness estimates on the scale up of double-fortified salt, however those that we did find suggest that the cost-effectiveness is moderate.

- Horton et al. (2011): The benefit:cost ratio of DFS was estimated as 2.4:1 if only the benefits to children and women were included, and between 4:1 and 5:1 if anemia levels for men were also included.
- Makkar et al. (2022): Based on their modeling that DFS can reduce iron deficiency anemia from 10.6% to 0.7% in men and 23.8% to 20.9% in women, and that men and women with iron deficiency anemia had lower wages by 25.9% and 3.9% respectively, they estimate that the economic benefit–cost ratio of introducing DFS at a national level is 4.2:1.

A1.5 Geographical mapping – Iron deficiency

In the table below we outline the top 15 countries in terms of the DALY rate per 100,000 from dietary iron deficiency. We highlight the countries that overlap with the countries we have identified as promising for fluoridation:

Country	DALY rate per 100,000
Mali	1,244.00
Zambia	1,092.58
Burkina Faso	1,014.58
Gambia	983.86
Bhutan	966.83
Yemen	923.89
Senegal	883.82

Chad	855.09
Nigeria	849.82
India	838.38
Pakistan	818.50
Niger	811.22
Somalia	794.68
Guinea-Bissau	766.54
United Republic of Tanzania	709.16

A2 Folic acid

A2.1 Precedent

Germany currently requires its salt to be fortified with folic acid (Marthaler et al., 2011).

Nutrition International is developing and introducing double-fortified salt with iodine and folic acid in Ethiopia (Nutrition International, 2022). Their program, spanning 2022-2025, will see the formulation and process of this double-fortified salt tested with local salt producers in Ethiopia, and will improve the evidence base of the benefits.

A2.2 Evidence of impact

We have been unable to find any studies evaluating the effectiveness of fortifying salt with folic acid in reducing neural tube defects. It seems that most studies conducted up to this point have focused on the feasibility of fortifying salt with folic acid, rather than its effectiveness.

We should follow Nutrition International's work in Ethiopia as they plan to "test and establish the benefits of salt double-fortified with iodine and folic acid".

2.3 Feasibility

Fortification of salt with folic acid seems feasible and unlikely to impact the organoleptic characteristics of salt, though we note that the addition of folic acid will increase the price of salt (Garrett and Bailey, 2018).

- Li et al. (2011): A feasibility study in Guatemala found that samples of salt fortified with folic acid retained >80% folic acid after nine months of storage at 40 °C and 60% relative humidity. However, it did note that one limitation of these matrices may be segregation (separation) of folic acid particles from the crystal of salt. Further research in this area is required.
- McGee et al. (2017): This study identified a new stable formulation of salt, fortified with both folic acid and iodine, that utilizes a single solution sprayed onto salt using standard salt iodization infrastructure and equipment. After fortification and 12 months of storage at ambient conditions, the formulations prepared using refined salt retained >80% of the folic acid and >90% of the iodine. For fine-grained salt, the appearance is likely acceptable owing to the pale, even dispersion of color; however, for coarse-grained salt, organoleptic issues may arise owing to unevenness of folic acid distribution, which needs to be addressed.

A2.4 Cost-effectiveness

We have been unable to find any existing cost-effectiveness estimates for fortifying salt with folic acid.

A2.5 Geographical mapping - Neural tube defects

In the table below we outline the top 15 countries in terms of the DALY rate per 100,000 from neural tube defects. We highlight the countries that overlap with the countries we have identified as promising for fluoridation:

Country	DALY rate per 100,000
Burkina Faso	967.72
Mali	948.39
Chad	914.12
Niger	849.88
Sierra Leone	786.16
Central African Republic	714.92
Nigeria	707.63
Afghanistan	689.07
Guinea	673.45
Benin	618.73

Somalia	542.40
South Sudan	504.00
Guinea-Bissau	463.20
Côte d'Ivoire	426.49
Haiti	407.47

A3 Multiple micronutrient fortification

A3.1 Precedent

There is currently no precedent for multiple micronutrient fortification in mandatory or voluntary salt fortification standards (Global Fortification Data Exchange, n.d.).

We have also not been able to find any NGOs working on this.

A3.2 Evidence of impact

We also find that multiple micronutrient fortification of salt isn't very well researched. The quality of evidence of the studies that we have managed to find is quite weak, with a small sample size and a tendency to measure indicators of deficiency (e.g., hemoglobin concentrations) rather than the actual prevalence of deficiency. We summarize the studies that we managed to find below:

- Kumar and Rajagopalan (2007): Salt fortified with multiple micronutrients – iron, vitamins A, B1, B2, B6, B12, folic acid, niacin, calcium pantothenate, and iodine – was used in the food cooked in the school kitchen for 63 students aged 7-11 (the control group were 66 students who did not eat at school) in Chennai, India. This study found that:
    - There was a significant ($p<0.05$) improvement in the experimental group in hemoglobin, red cell count, urinary iodine and serum vitamin A, whereas in the control group there was a statistically significant decline ($p<0.05$) in hemoglobin, hematocrit, red cell count and urinary iodine.
    - Angular stomatitis was eliminated from baseline 30.4% in the experimental group, whereas it increased from 3.25% to 25.5% in the control group.

  - In 4 out of the 7 memory tests, and in the letter cancellation test for attention, the mean increment in scores in the experimental group is significantly more ($p<0.05$) than the control group.
  - There was no significant improvement in overall intelligence between the experimental and control groups.
- Vinodkumar et al. (2009): An RCT in Indian schools evaluating salt fortified with vitamins A, B1, B2, B6, B12, folic acid, niacin, iron, iodine, and zinc vs salt fortified with iodine. The salt was used in all meals prepared for the children at school. Post-intervention in the experimental group there was a significant improvement ($p<0.05$) in all the biochemical measurements. The increase in hemoglobin was 0.67 g/dL. Iron status and body iron stores increased significantly in the experimental group compared to the control group, while serum zinc increased by 50 mg/dL, and the prevalence of retinol deficiency decreased from 57.1 % at baseline to 16% post-intervention. There is also a positive indication of the impact of multiple micronutrient fortification on memory and improved test scores.
- Zimmermann et al. (2004): Adding triple-fortified salt (salt fortified with iodine, iron, and vitamin A) to the food of children aged 6-14 in place of iodized salt increased mean hemoglobin by 15 g/L at 10 months follow-up ($P < 0.01$), iron status indexes and body iron stores improved significantly ($P < 0.05$), and mean serum retinol, retinol-binding protein, and the ratio of retinol-binding protein to prealbumin increased significantly ($P < 0.01$). Also at the 10 month follow-up, prevalences of vitamin A deficiency and iron deficiency anemia were significantly lower in the experimental group than in the control group ($P < 0.001$).
- An upcoming study sets out to evaluate the nutritional impact of salt fortified with iron (in the form of ferric pyrophosphate), zinc, vitamin B12, folic acid, and iodine vs salt fortified with iron (in the form of encapsulated ferrous fumarate), zinc, vitamin B12, folic acid, and iodine vs iodized salt for the improvement of micronutrient status among non-pregnant women of reproductive age and preschool-aged children in Punjab, India. Fortified salt will be used in place of their usual salt. The change in the mean concentration of various MN biomarkers will be considered primary outcomes.

A3.3 Feasibility

The overall feasibility of salt fortified with multiple micronutrients seems quite high, as does acceptance of this salt.

An acceptability survey in Tanzania found that quadruple-fortified salt (salt fortified with iron, iodine, vitamin B12, and folic acid) and double-fortified salt (salt fortified with iron and iodine), are equally acceptable and have similar sensory scores as standard iodized salt. The overall acceptability for the salts were as follows: quadruple-fortified salt (82%) > iodized salt (79%) > double-fortified salt (78%). The mean sensory (taste, color and appearance) scores for the salts were as follows: quadruple- and double-fortified salt (1.7) > iodized salt (1.6) (Mdoe et al., 2023).

A study in Nigeria found the fortification of salt with iron, iodine, folic acid, and vitamin B12 – where iron and vitamin B12 are added as encapsulated particles (premix) and iodine and folic acid are added as a solution – can use existing facilities for making double-fortified salt (salt fortified with iron and iodine) without any change in equipment (Modupe and Diosady, 2021). Therefore, it likely presents a cost-effective approach for delivering multiple micronutrients to vulnerable populations, as the additional cost of adding these micronutrients to salt is about $0.30 per year per person. However, the study did note that the folic acid discolored the salt to a yellow color which may reduce consumer acceptability. This will need to be tested further.

A novel spray-cooling technique to build microcapsules containing iodine, iron, and vitamin A was used to add these micronutrients to salt in Africa. Zimmerman et al. (2004) found that this method of fortification is promising, and that iodine, iron, and vitamin A are highly stable when added to local African salt in this way. After six months in storage, losses of iodine and vitamin A in the salt were ≈12–15%, and color was stable.

A3.4 Cost-effectiveness

We have been unable to find any existing cost-effectiveness estimates for fortifying salt with multiple micronutrients.

A4 Conclusions

The best case can be made for adding iron, on top of iodine and fluoride, to salt in terms of precedent, feasibility, and evidence base. It's less clear for folic acid fortification or multiple micronutrient fortification whether we can make a case for a new charity to work on this yet, mostly based on a much weaker evidence base (particularly for folic acid).

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