Response to two health-related themes expressed in the survey

by Gary D. Slade

Table of Contents

1. "Fluoride is Only Effective Topically"

1.1. Synopsis

- On average, throughout people's lifespan, most of the dental health benefits of fluoridated water are due to TOPICAL effects of the fluoride in preventing decay.
- The remaining benefit is due to pre-eruptive effects that occur when fluoride is incorporated into unerupted teeth as they are forming under the gums during childhood.
- Topical effects and pre-eruptive effects account for approximately equal portions of the preventive benefit in childhood, whereas in adulthood, the benefit is entirely due to topical effects.
- People experience the greatest preventive benefit when they experience both effects which happens when fluoridated water is consumed in childhood and throughout life.

1.2. Plain language summary

Throughout people's lifespan, fluoride in drinking water prevents dental decay mostly because of its topical effects on teeth that have erupted. This is called the post-eruptive effect. The remaining preventive benefit is due to fluoride being incorporated into unerupted teeth as they are forming under the gums during childhood. This is called the pre-eruptive effect.

When dental health benefits of fluoride were first discovered in the 1930s and 1940s, it was assumed that preventive effect was mostly pre-eruptive. It wasn't until the 1960s, when fluoride was first added to toothpaste, that researchers discovered that decay could be prevented by topical effects of fluoride on erupted teeth. Subsequent laboratory research and population studies showed that fluoride in drinking water has topical effects (in addition to its pre-eruptive effects). Those studies found two ways in which fluoride in drinking water prevents decay topically, on erupted teeth. Firstly, while the fluoridated water is in the mouth, some of the fluoride comes into contact with the soft dental plaque that occurs naturally on the tooth surface. The second topical effect comes from fluoridated water that is swallowed. Some of it then enters the saliva via the bloodstream, which means the fluoride as another opportunity to become concentrated in dental plaque on the tooth surface.

By the end of the 20th century, when the topical and pre-eruptive effects of fluoride in drinking water were better understood, most researchers concluded that the main preventive effect of fluoridated drinking water was topical. One piece of evidence came from studies of people who started consuming fluoridated water as adults. By then, all of their permanent teeth had erupted, meaning that the preventive benefit of fluoridated water was due solely to post-eruptive effects. The fact that those adults developed decay at a lower rate than adults who lived in non-fluoridated areas indicated that fluoride in drinking water could prevent decay solely on account of its topical effects on erupted teeth.

However, those same studies found that decay rates were even lower in adults who had consumed fluoridated water in childhood AND in adulthood. This greater benefit from LIFETIME consumption of fluoridated water occurs because of the additional pre-eruptive effects of fluoride during childhood. It's difficult to be precise as to just how much additional benefit occurs because of the pre-eruptive effect in childhood. The best evidence in humans comes from a study of over 17,000 children aged 6-15 years who provided a lifetime history of their water consumption. Decay rates were measured in the first permanent molars, which erupt around six years of age. The study showed that fluoride in drinking water had an overall preventive benefit, reducing decay in by 28% overall, with about half of the effect being pre-eruptive and one half post-eruptive. In other words, the topical effect was equivalent to the pre-eruptive effect in this age group.

<u>1.3. Detailed response</u>

Cariologists recognize two biological mechanisms by which fluoride affects the dental caries process.[1]

a) The pre-eruptive mechanism occurs when fluoride from the bloodstream is incorporated into a developing tooth, altering its mineral structure, making it more resistant to acid-dissolution when the tooth later erupts. Because most calcification of the primary teeth occurs *in utero*, the contribution of the pre-eruptive mechanism to caries prevention in the primary dentition is dependent predominantly on the amount of fluoride ingested by the mother during pregnancy. In contrast, most of the mineralization of developing permanent teeth occurs from birth to about eight years of age, and hence the contribution of the pre-eruptive mechanism to caries prevention in the permanent dentition is dependent predominantly on the amount of fluoride ingested during early childhood.

b) The post-eruptive mechanism occur when fluoride in the mouth comes into contact with erupted teeth. This is aided by fluoride's affinity for dental biofilm (i.e., "dental plaque", the film of salivary components that adhere to a tooth surface and the microbes that grow in the film). Fluoride is selectively concentrated in biofilm affecting two process critical to dental caries: (i) fluoride in biofilm inhibits acid-demineralization of enamel and increases the efficacy of re-mineralization, and (ii) fluoride in biofilm inhibits bacterial enzymes, and hence acid production by those bacteria. The contribution of these post-eruptive mechanisms to caries prevention potentially can occur from the moment of tooth eruption and throughout life.

1.3.1. Methods of administrating fluoride for caries prevention

Fluoride consumed via drinking water or in beverages and foods containing water is often characterized as a "systemic" method of administration because the intention is that the fluoride be swallowed. (That same is true for fluoride delivered in tablets, supplements, and in fortified salt and milk.) Alternatively, fluoride in toothpaste is often characterized as a "topical" method of administration because the intention is that it be spat out, not swallowed, after use. (The same is true for fluoride delivered in mouthrinse and professionally-applied products.)

1.3.2. Method of administration does not neatly distinguish between biological mechanisms of action

Most of the fluoride administered in drinking water or in foods or beverages prepared with fluoridated water is swallowed. At first appearance, this, suggests that its caries prevention via this mode of administration is due solely to pre-eruptive effects of the fluoride. However, that is a misnomer for two main reasons:

- some of the fluoride is not swallowed; instead, it is concentrated in the biofilm of erupted teeth in the mouth during consumption; and
- when ingested on a daily basis, the consumed fluoride increases the concentration of fluoride in circulating plasma which, in turn, increases the concentration of fluoride in the saliva,[2] with the fluoride then being concentrated in the biofilm of erupted teeth in the mouth.

Conversely, it is almost inevitable that some of the fluoride in toothpaste and other topically-applied products is swallowed, and if that occurs in childhood, it contributes to the pre-eruptive mechanism of caries prevention. However, the amount of fluoride swallowed during tooth brushing varies considerably among children,[3] making it difficult to quantify the overall contribution of toothpaste to pre-eruptive effects of fluoride occurring in the population.

1.3.3. Evolution of evidence concerning the relative contribution of pre- and post-eruptive effects

According to the biological reasoning outlined above, fluoride in drinking water can, in principle, prevent dental caries via a pre-eruptive mechanism, post-eruptive mechanism, or both mechanisms. Scientific thinking has changed considerably over the decades as to the relative contribution of each mechanism, reflecting the evolution in research about dental health effects of fluoride itself.

By the middle of the 20th century, it was assumed that that the caries-preventive effect of fluoridated drinking water was due entirely to pre-eruptive mechanisms. The evolution of this thinking aligned with sequence of discoveries about fluoride and dental health made in the first half of the century.[4] In summary: (i) Colorado brown stain was found to be endemic in some communities, but absent in others; (ii) co-incidentally, where Colorado brown stain was endemic, rates of dental caries were noticeably lower; (iii) further studies established that Colorado brown stain was attributable to the community's drinking water, specifically in children who had consumed the drinking water since birth; (iv) high concentrations of fluoride in the drinking water were then isolated as the cause of Colorado brown stain, which was renamed dental fluorosis; (v) further studies established that lifetime exposure to lower levels of fluoride in drinking water of around 1 mg/L F was associated with lower rates of dental caries compared to a negligible concentration, and with little significant dental fluorosis; (vi) in subsequent intervention studies that added around 1 mg/L F to drinking water, dental caries experience was lessened in cohorts born after implementation of fluoridation; (vii) by then, it had been established that high concentrations of fluoride in drinking water affected the developing teeth to cause dental fluorosis seen in epidemiologic studies; (viii) by deduction, it was reasonable to believe that caries preventive benefits of lower concentrations of fluoride in drinking were likewise due to its effects on the developing enamel.

In fact, there was already some evidence to question the assumption that fluoride prevented caries solely be a pre-eruptive mechanism. In the Grand-Rapids study, caries experience of 16 year olds 10 years after implementation of fluoridation was lower than the level seen prior to fluoridation. Commenting on the significance of this finding, Arnold alluded to a post-eruptive effect of water fluoridation noting “It is to be remembered that these children in most cases were those who presumably had the coronal portion of their permanent teeth already calcified when fluoridation started.”[5]

By the 1960s, the premise that fluoridated water prevented caries predominantly via a pre-eruptive mechanism was being challenged by biological studies. In one study of 36 premolar teeth extracted for orthodontic reasons, there was little correlation between fluoride concentration of surface enamel and caries experience of the study participants' other teeth.[6] Although a larger study reported an inverse correlation,[7] the finding cast into doubt the prognostic importance of fluoride’s incorporation into surface enamel. This was around the time that randomized controlled trials of topically-applied fluorides were showing clear evidence of efficacy, representing proof-of-principle that fluoride's post-eruptive mechanisms of caries prevention could be significant. There was also a marked increase in microbiological, in-vitro, and animal-experimental studies of post-eruptive mechanisms in dental caries. By the 1980s, a narrative review of the limited epidemiologic evidence and the extensive biological studies concluded that the "major cariostatic effect of water fluoridation, fluoride tooth paste and mouth rinses can probably be ascribed to regular increases in fluoride ion activity in the oral fluids".[8]

The first persuasive epidemiological study to address the question came from re-analysis of data from the Tiel-Culemborg study.[9] A unique feature of the study was its recording of pre-cavitated carious lesions (in addition to the conventional recording of caries experience at the level of cavitation). The re-analysis first confirmed the original finding[10] that fluoridation was associated with a significant benefit in preventing caries at the cavitation threshold. However, when pre-cavitated lesions were included in the re-analysis, caries experience in fluoridated Tiel did not differ appreciably from non-fluoridated Culemborg.[9] The author concluded that fluoridated water did not alter the total caries attack rate (manifesting as pre-cavitated AND cavitated caries), and deduced that difference in cavitation-level caries must have been due to a post-eruptive effect, namely, that fluoride from drinking water favored remineralization of initial, pre-cavitated lesions, preventing their progression to cavitated lesions. By the turn of the century, another prominent narrative review concluded that the predominant caries-preventive effect of fluoridated drinking water was through post-eruptive mechanisms.[11] This represented an evolution in scientific thinking that was characterized as a "paradigm shift".[1]

This century, the "predominantly post-eruptive" explanation for caries preventive benefits of fluoridated water has been corroborated by findings from two groups of epidemiologic studies:

- In studies of children conducted this century, [12-15] _ENREF_66_ENREF_69_ENREF_73 sequential cross sectional studies conducted during a relatively short period after a change in community water fluoridation (i.e., addition or removal of fluoride) reported changes in caries experience even in age-groups born years before the change in fluoridation. Because pre-eruptive mechanisms are an implausible explanation in such children, the observed trends in disease that are best explained in terms of post-eruptive effects of water fluoridation.
- In studies of adults conducted this century, [16-21] _ENREF_81_ENREF_82_ENREF_83_ENREF_84_ENREF_85 greater lifetime exposure to fluoridation was associated with less caries experience, even among those born approximately one decade or more after implementation of fluoridation. Again, because pre-eruptive mechanisms are an implausible explanation, the observed trends in disease that are best explained in terms of post-eruptive effects of water fluoridation.

The more persuasive evidence comes from epidemiologic studies that were designed specifically to test hypotheses about relative contributions of pre- and post-eruptive effects. One is the study summarized above, that re-analyzed the Tiel-Culemborg data, demonstrating that fluoridation prevented caries by promoting remineralization of initial carious lesions - a hallmark of post-eruptive mechanisms.

However, the other epidemiologic studies investigating relative contributions provide evidence favoring the *pre*-eruptive mechanism. Three such publications[22-24] re-analyzed data from a single survey[25] in which each child's periods of exposure- and non-exposure to fluoridated water were determined retrospectively. The re-analysis was restricted to first-permanent molars because they have an established chronology of crown mineralization during the first eight years of life, and because caries occurs most frequently in first molars. Residency in fluoridated areas during and after defined-periods of mineralization of first molars were used to classify exposure periods that plausibly are dominated by pre- or post-eruptive caries-preventive mechanisms. The analysis further investigated potential differences according to the anatomical location of caries on the tooth, and according to exposure during discrete phases of mineralization. The findings were consistent in showing that both pre- and post-eruptive mechanisms of caries prevention were necessary to explain observed caries preventive benefits of water fluoridation. Specifically:

- Considering overall caries experience of first permanent molars, pre-eruption exposure was required for a caries-preventive effect whereas exposure only after eruption did not lower caries levels significantly;[23]
- More detailed analysis of the period of pre-eruptive exposure showed that exposure during crown completion was important for caries prevention irrespective of the effect of exposure at crown maturation and at post-eruption.[24]

- More detailed analysis of the anatomical location of dental caries found that, in surfaces with pits and fissure, greater pre-eruption exposure reduced caries levels significantly, whereas at other tooth surfaces, both high pre- and post-eruption exposure were required to prevent caries.[22]

Another epidemiologic study designed specifically to test hypotheses about pre- and post-eruptive mechanisms was a cross-sectional study of n=1,485 South Korean children sampled either from an intervention community that ceased fluoridation seven years earlier or a comparison community that had never been fluoridated.[26] Among 11 year olds, caries experience was lower in the intervention community (where the children had been exposed to fluoridation for the first four years of life) than in the control community. This was in contrast to equivalent levels of caries experience observed in the primary dentition, suggesting that the two communities had a similar risk for developing caries after cessation of fluoridation. The results in the permanent dentition are consistent with fluoridation in the intervention community producing a pre-eruptive effect that conferred caries-protection seen several years later, after the teeth erupted despite being unexposed to fluoridation after eruption.

Another relevant consideration is the 2011 Cochrane systematic review of fluoride supplements.[27] It concluded that "use of fluoride supplements is associated with a reduction in caries increment when compared with no fluoride supplement in permanent teeth." This is relevant because virtually all fluoride in fluoride supplements is swallowed, and because the recommended schedule is that they be discontinued within a few years after the permanent teeth first erupt. Hence, their observed caries preventive benefits must be due almost entirely due to pre-eruptive effects. Likewise, there is some evidence that fluoride supplementation of milk is effective in preventive caries,[28, 29] with studies suggesting that both pre- and post-eruptive mechanisms account for the effect.[30]

1.3.4. Critical appraisal of pre- and post-eruptive caries-preventive effects of fluoride in drinking water

The initial belief that fluoridation prevented caries solely via pre-eruptive mechanisms was a deduction based on the historical epidemiologic studies that discovered fluoride's contributions to both dental fluorosis and dental caries. The subsequent "paradigm shift" in thinking that favored a predominantly post-eruptive mechanism occurred near the end of the 20th century. It was based on an upsurge in biological studies and re-analysis of the historical epidemiologic data. This century, new studies of adults and other studies designed specifically to test relative contributions of each mechanism offer support for the pre-eruptive mechanism. Also, findings from studies of fluoride supplements and milk fluoridation provide in-principle support that pre-eruptive mechanisms are important for population-level prevention of dental caries.

Overall, the studies of caries preventive mechanisms support a combination of pre-eruptive and post-eruptive effects of fluoride in drinking water. Over time, scientific opinion has altered as to whether the "predominant" contribution is via one or the other mechanism, with studies this century suggesting that it is probably a draw. Logically, the share attributable to pre-eruptive effects is greatest in childhood (where little time has elapsed in order for a post-eruptive effect to accrue) and it is necessarily predominant in adulthood. It seems unlikely that any single biological experiment or observational epidemiological study will resolve the question definitively. Instead, the most defensible conclusion is that both mechanisms are important in understanding caries preventive benefits of fluoridation. It follows that the greatest caries-preventive benefit is achieved when both mechanisms operate, which occurs for individuals who have lifetime exposure to fluoridation.[4]

2. "Fluoride is Not Science Based"

2.1. Synopsis

- There is more than a century of scientific evidence supporting addition of fluoride to drinking water, toothpaste and other dental health products in order to prevent dental decay.
- Nowadays, as new evidence is gathered, it is re-evaluated periodically using systematic reviews and meta-analysis.
- These represent the most rigorous method to assess scientific evidence concerning human health and healthcare.
- Consistently, those systematic reviews endorse water fluoridation as a safe and effective method to prevent dental decay in the U.S. population.

2.2. Plain language response

Observational epidemiologic studies of children covering more than half a century provide compelling and consistent evidence that fluoride in drinking water is associated with substantial benefits in preventing dental caries. The benefits are seen in the primary and permanent dentitions, with the magnitude of relative benefit being greater in the former. Statistical analytic methods used in recent decades account for other sources of fluoride—such as toothpaste—and other factors that influence dental caries in populations such as race, ethnicity, parental income and education. Those studies also demonstrate a caries-preventive benefit of water fluoridation even in populations where virtually all children use fluoridated toothpaste. The most recent U.S. evidence, reported in 2018, is from a study of a nationally-representative sample of children and adolescents that found a substantial preventive benefit, both in the permanent and primary teeth. Notably, benefits were more pronounced for children in low-income families than in high-income families. Similar studies of adults likewise show that water fluoridation is associated with reduced extent of dental caries.

Evidence from observational studies fulfills all criteria for a causal interpretation that water fluoridation prevents caries:

- Findings are *consistent*, over time and in different populations;
- The *strength of association* is of public health importance, typically in the range of 30-40% reductions in caries;
- The preventive association applies *specifically* to dental caries, not to other oral diseases;

- Studies establish the required *temporal sequence* between exposure to the fluoridation and caries prevention;
- There is a *biological gradient* in which the benefit increases with increasing extent of exposure to fluoridation;
- Results are *analogous* to caries-preventive effects of other (non-water) sources of fluoride;
- Several features of an *experimental study* are reproduced in studies of fluoridation; and
- The causal interpretation is *biologically plausible*, with good evidence that dental caries prevention is due to a combination of pre-eruptive mechanisms (i.e., incorporation of fluoride into developing enamel which becomes more resistant to subsequent acid attacks) and post-eruptive mechanisms (i.e., concentration of intra-oral fluoride in dental biofilm, inhibiting demineralization and enhancing remineralization).

This evidence from observational studies is bolstered by findings from prospective, community-level intervention studies, showing greater reductions in decay rates in communities that implement fluoridation compared to communities that remain non-fluoridated. Most studies that have assessed changes following cessation of fluoridation report an increase in dental caries compared to comparison communities.

2.3. Detailed response

2.3.1. Early scientific findings

The scientific discovery that fluoride in drinking water prevents dental caries has been described as a "classic epidemiological study".[4] It began with studies of a completely different dental condition, now known as dental fluorosis, and which was first described in the early 20th century as "mottled" teeth and "Colorado brown stain". By the 1920s, dentist in the U.S. Public Health Service observed that dental caries occurred infrequently, if at all, in children with mottled teeth. In contrast, at that time, dental caries was rampant in children unaffected by mottling. With the aid of the new photospectrographic method of measuring fluoride concentration, new epidemiologic studies investigated the association between concentration of fluoride in drinking water and dental caries.

2.3.2. U.S. Public Health Service studies conducted in the first half of the 20th century

The first observational study of an association between exposure to fluoride in drinking water and dental caries was reported by Dean in 1938.[31] It compared dental caries of nine-year olds exposed to 0.6-1.5 mg/L F or 1.7-2.5 mg/L F in drinking water, with the analysis limited to continuous residents of the six cities studied. In the primary dentition, the prevalence of dental caries (i.e., children having 1 or more teeth with caries experience) was 69 percent among those exposed to the higher concentration compared to 89 percent among children exposed to the lower concentration. In the permanent dentition, prevalence was 51 percent and 74 percent, respectively.

By 1942 Dean and co-investigators reported associations between dental caries and fluoride using data from 21 cities where the concentration of fluoride in drinking water ranged from undetectable amounts to 2.6 mg/L F.[32] Dental examiners also assessed dental fluorosis. When examined ecologically (i.e., by plotting community-average levels of caries and community-average levels of fluorosis), the findings identified a range of 1.0-1.2 mg/L F as the "optimal" concentration at which the occurrence of dental caries was lessened, but without elevated prevalence of dental fluorosis. Chapter 23 of Burt et al[4] summarizes this extensive set of studies, commenting on their strengths, limitations and implications.

Those association studies provided the rationale for subsequent intervention studies designed to determine if dental caries could be prevented by adding fluoride to drinking water. The first such study was conducted in Grand Rapids, MI, where fluoride was added to the public water supply to a concentration of 1mg/L in 1945. In that year, epidemiologists conducted dental examinations of 28,614 school children, virtually the entire child population of the city at the time. After fluoridation, they repeated examinations annually for 10 years, selecting samples of children from five school grades in each year (i.e., not necessarily the same individuals from one year to the next). Five years after fluoridating the water, mean deft index in the primary dentition reduced by one third in 5 year olds who were continuous residents (and who represented 73% of the population).[33] After 10 years, the mean DMFT index in the permanent dentition had halved in 12-year-olds.[34] In contrast, over the same period, dental decay levels reduced by less than 20% in samples of continuous residents of non-fluoridated Muskegon, MI, where Dean and colleagues likewise conducted annual dental examinations. By 1946, studies to evaluate fluoridation were underway in four other pairs of cities in Illinois, New York, Canada and the Netherlands. Results were published in the 1950s, replicating the effects seen in the Grand Rapids-Muskegon study (Table 1).

Table 1: Summary of findings from children aged 14-15 years in five intervention studies*

Country (baseline year)	United States (1947)	United States (1946)	United States (1944)	Canada (1944)	Netherlands (1952)
Test city	Grand Rapids	Evanston	Newburgh	Brantford	Tiel
Control city	Muskegon	Oak Park	Kingston	Sarnia	Culemborg
Mean DMFT: Test city	12.4	11.3	10.4	8.0	13.9
Mean DMFT: Control city	6.2	5.9	6.0	3.9	6.8
% difference	50	48	42	51	51

Data are from Backer-Dirks[35] and Ast and Fitzgerald[36] as tabulated in the 1991 National Health and Medical Research Council report[37]

2.3.3. Studies and narrative reviews in the second half of the 20th century and the first decade of the 21st century

In 1962, based primarily on evidence from studies discussed above, the U.S. Public Health Service first recommended fluoridation of public water systems to prevent dental caries.[38] Communities responded quickly, and by 1970, 49% of the U.S. population was served by a fluoridated public water system.[39] This rapid spread of fluoridation motivated a new round of observational epidemiologic studies, both in the U.S. and in other countries that had adopted fluoridation.

There are three comprehensive narrative reviews that evaluated studies in children during the period: a) one was a review of 55 studies reported primarily before the 1980s;[40] b) another review assessed 24 studies reported between the late 1970s and 1980s;[41] and c) another review focused primarily on 58 studies reported after 1990.[42] In each instance, the reviews concluded that children living in communities with fluoridated water had significantly less dental caries that children living in non-fluoridated areas.

2.3.4. Systematic reviews of dental caries preventive effects of fluoridated drinking water in children

The reviews cited above[40-42] are nowadays classified as *narrative* reviews to distinguish them from *systematic* reviews. The distinguishing features are methodological: systematic reviews begin by defining a structured research question; strategies to search bibliographic sources and database are then specified; before the search, criteria are developed for inclusion and exclusion of studies; researchers conduct an initial review of study titles and abstract to determine those that meet selection criteria; and each study is synthesized according to a checklist of features that appraise the quality of the studies. The compiled review summarizes findings, comments on the scientific quality of each study, and creates tabular and graphical summaries. In some instances, systematic reviews combine results from two or more studies using meta analysis, a statistical method that pools quantitative results published from different studies. Methods for systematic reviews were first developed in the 1990s, spearheaded by the Cochrane collaboration, which aims to improve rigor in evaluating healthcare, and in particular, the results from clinical trials comparing treatments. While any researcher with the requisite skills and resources can conduct a systematic review, reviews undertaken by the Cochrane collaboration are often valued for their rigor and objectivity.

The criteria used to select studies and rate their methodological quality are critical components of systematic reviews. Virtually all systematic reviews use a similar "hierarchy of study designs" when judging quality of the evidence: properly conducted randomized controlled trials are at the top of the hierarchy, observational studies are given lower quality ratings, and case reports or expert opinions are at the bottom of the hierarchy. Nonetheless, systematic reviews vary in the details and application of the evidence hierarchy. For example, a recent Cochrane review of water fluoridation applied GRADE criteria to evaluate quality of studies, commenting that “when applying GRADE to non-randomised studies, the quality of the evidence automatically starts at ‘low’, as opposed to ‘high’.” [43] In contrast, the U.S. Preventive Services Task Force considers a broader set of characteristics in rating the quality of evidence, particularly when evaluating preventive public health interventions for which randomized trials are not feasible.[44]

The first systematic review of fluoridation was conducted in 2000 by the United Kingdom’s National Health Service Centre for Reviews and Dissemination.[45] The research question was defined thus: “What are the effects of fluoridation of drinking water supplies on the incidence of caries”. While the search criteria placed no historical restrictions on studies to be reviewed, only 26 met the investigators’ inclusion criteria which stipulated that studies had to report changes in caries over time, comparing one community where fluoride was added to or removed from drinking water with a control community that did not change its fluoridation status. Specifically, it required that communities be assessed at “two points in time, one of which is less than one year since the change of water fluoridation status in one of the groups”. The review, which included meta analysis to quantitatively combine the published results, concluded that introduction of fluoridation was effective in reducing dental caries, with the mean difference between communities in changes in dmft/DMFT ranging from 0.5 to 4.4 teeth per child. The review also found that withdrawal of water fluoridation led to an increase in prevalence of caries. It noted that most of the included studies were of moderate quality (level B). That rating was driven by the fact that there have been no randomized controlled trials of fluoride in drinking water for dental caries prevention. Instead, the 26 studies reviewed used observational study designs which ranked lower in the evidence hierarchy applied by the reviewers when evaluating quality.

Other systematic reviews soon followed, although they varied in the number of studies reviewed. A 2007 review by Australia's National Health and Medical Research Council updated the U.K. review with two additional studies, concluding that introduction of fluoridation reduced cares while removal of fluoridation increased caries.[46] In 2013, the U.S. Community Preventive Services Taskforce updated the U.K. review with its own evaluation of 28 studies, endorsing fluoridation "based on strong evidence of effectiveness in reducing dental caries across populations."[47] It also found that fluoridation was effective in reducing caries across all socioeconomic groups. Meanwhile, a review of systematic reviews and practice guidelines concluded that water fluoridation is effective in reducing caries in children, with some evidence that it can "reduce the oral health gap between social classes."[48]

In contrast, the 2015 review by the Cochrane collaboration was more restrictive than other systematic reviews, using results from only nine studies that evaluated primary dentition caries following addition of fluoride to drinking water, and 10 studies that evaluated permanent dentition caries.[43] Although it concluded that fluoridation led to a 35% reduction in dmft and a 26% reduction in DMFT, it found that all studies had a high risk of bias. It also found insufficient evidence to determine the effect of stopping water fluoridation or the effect of fluoridation on dental health disparities.

2.3.5. Studies of fluoridation and dental caries in children reported since the 2015 Cochrane systematic review

Several new epidemiologic studies of children have been reported since the Cochrane review, as summarized in Table 2. Each study found dental caries preventive benefits associated with exposure to water fluoridation. Results therefore are consistent with the main finding of the reviews summarized above.

Table 2: Studies reported since the 2015 Cochrane systematic review

Year(s) and setting for data collection	Methods (row 1) Results (row 2)
1986 to 2003 Brazil, DMFT of 12-yr-old children [12]	Time-series analysis of ecological data (550 records from 428 locations) linked to area-level measures of fluoridation and socio-economic status.
	Compared to non-fluoridated communities, mean DMFT was 0.94 lower in fluoridated communities.
1999-2008 and 2011-2012 Australia, dmft of 4-9 yr olds [13]	Sequential cross-sectional surveys of dental examination and radiograph records recorded pre-fluoridation (1998-2008; n=201) and 3-years post-fluoridation (2011-2012, n=256) n= children living in a remote Indigenous community of Australia before (n=393) and after fluoridation (n-263).
	Significant three year reductions in mean dmft (4.54 to 3.66).
1999-2014 United States, dmfs and DMFS of 2-17 yr olds[49]	National, cross-sectional surveys of 16,718 children whose county-of-residence was classified according to percentage of the population served by community water fluoridation.
	Mean dmfs of 2-8 yr olds was less in counties with ≥75% of population served by fluoridated water (mean =3.3) than in counties with <75% of population served by fluoridated water (mean = 4.6). Mean DMFS of 6-17 yr olds was likewise lower (1.9 versus 2.2, respectively)
1999-2014 United States, dmfs and DMFS of 2-17 yr olds [50]	National, cross-sectional surveys of 16,718 children listed above, where household income-to-poverty ration was used to compute absolute- and relative measures in income-related inequality in caries.
	In the primary dentition, there was a statistically significant interaction between county-coverage of fluoridation and income that attenuated the income-gradient in dental caries. In the permanent dentition, the gradient was also attenuated, but no to a statistically significant degree. (See Figure 1)
2003 and 2008, Alaska, Medicaid claims for dental caries treatment	Medicaid dental treatment claims for 0-18 yr olds analyzed in 2003 (n = 853) during fluoridation and five years later (n = 1052), five years after cessation of fluoridation.
	Following cessation of fluoridation, there were significant increases number of caries-related procedures per child (2.35 vs. 2.02) and in treatment costs (varying according to age group from 28% to 111%.
2005 and 2012, Australia, dmft and DMFT of 4-12 yr olds [14]	Sequential cross-sectional surveys of children living in a remote Indigenous community of Australia before (n=393) and after fluoridation (n-263).
	Significant seven-year reductions in mean dmft (4.44 to 2.76) and mean DMFT (2.08 to 1.32)
2008-2012, Australia, dmft of 5-7 year olds [51]*	Three sequential cross-sectional surveys in one city before and after fluoridation (average n=827 per survey year) and in a control location which had no fluoridation throughout (average n=610 per survey year)
	Four-year reduction in mean dmft was greater in city that implemented fluoridation (2.02 to 0.72) than in non-fluoridated comparison area (2.09 to 1.21)
2011-2012 Australia, dmft and DMFT of 5-12 year olds[52]	Cross-sectional study of 10,825 children classified as living either in the fluoridated metropolitan area or the non-fluoridated south-west area of Western Australia
	Mean dmft was significantly greater in non-fluoridated (e.g., 5-yr-old dmft=1.6) than fluoridated area (5-yr-old dmft =1.1). Mean DMFT was greater, though not statistically significantly so, in non-fluoridated (e.g., 12-yr-old DMFT=0.82) than in fluoridated area (12-yr-old DMFT=0.60)
2012-2014, Australia, income-inequality in dmfs and DMFS of 5-14 yr olds [53]	National, cross-sectional study of 21,328 children classified as living either in the fluoridated or non-fluoridated areas; absolute measure of income inequality in dental caries computed as the regression-slope index of inequality
	Absolute income-related inequality in dmfs of 5-9 yr olds was less in fluoridated areas (−4.18) than in non-fluoridated areas(–6.20). Absolute inequality in DMFS of 9-14 yr olds was less in fluoridated areas (−0.60) than in non-fluoridated areas(–1.66)
2009-2014, Canada, socioeconomic inequalities in caries of grade 2 children[15]	Sequential cross-sectional surveys in 2009-10 (n=511) when Calgary water was fluoridated and in 2013-14, (n=2980), 2-3 years after defluoridation. Socio-economic inequities in dmft and DMFT gradients were computed according to a) small-area measures of socio-economic deprivation; and b) dental insurance
	Inequities in caries experience according to dental insurance status and by small area material deprivation were more apparent in 2013/14 than in 2009/10.
2009-2012, England, multiple caries-related outcomes in children [54]	Cross-sectional, ecological analysis of n= 32,482 local statistical areas, 12% of which were fluoridated. Dental caries measured in 5-year-olds (dmft) and 12-year olds (DMFT) in the National Dental Epidemiology Program. Rates of dentally-related hospitalization were from national hospital episode statistics (HES) for children aged 1-4 years.
	After adjustment for ethnicity and socio-economic deprivation, there was 28% lower likelihood of dental caries in fluoridated areas versus non-fluoridated areas for 5-year olds, and 21% lower likelihood for 12-year olds. Fluoridated areas had 45% fewer dental-caries related hospital admissions of 1-4 year olds compared to non-fluoridated areas.
2015, South Korea education-inequality in dmf	Examination survey of 6-, 8- and 11-year-old South Korean children living in fluoridated Okcheon and non-fluoridated Yeongdong. Questionnaires determine educational attainment of parents.
	Education-associated inequalities in dental caries were statistically significant in Okcheon but absent in Yeongdong.

* Prior to publication, results from this study were used in the Cochrane systematic review

The studies in Table 2 include time-series cross-sectional studies in communities that either added or removed fluoride from drinking water. Others used a single-cross sectional study design, focusing on the association between exposure to fluoridation and the extent of income-inequalities in caries. One study warrants further emphasis because of its timeliness in being the first study in 30 years to investigate water fluoridation and dental caries in the U.S. child population. The cross-sectional study used data from five cycles of the National Health and Nutrition Examination Survey (NHANES) conducted between 1999 and 2014. Dental caries experience of 16,718 sampled children was measured by trained examiners who recorded dfs and DMFS indices. Sociodemographic characteristics and dental health behaviors were reported by parents/guardians during the NHANES interview. Information about fluoridation in each child's county-of-residence was obtained from the Water Fluoridation Reporting System (WFRS). This database contains information about fluoride concentration and population size served by each of approximately 54,000 U.S. public water systems.

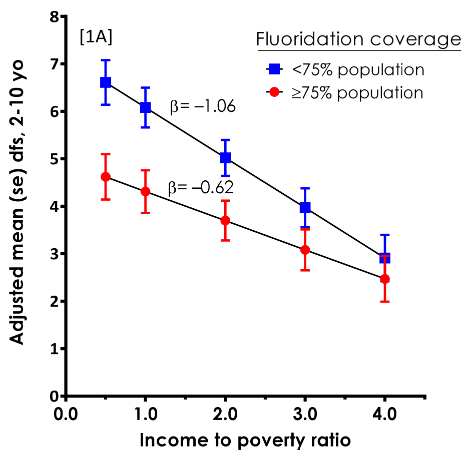
The first publication from the study compared caries experience according to the percentage of county population served by a fluoridated public water system. For descriptive purposes, mean levels of caries experience were compared between two groups classified according to the percentage of county population served by public water containing ≥0.7 mg/L F: <75% or ≥75%. Separate analysis used a linear regression model to estimate a "dose-response" gradient between caries experience and the proportion of the county's population that was fluoridated (modeled as a continuous variable, ranging from 0 to 1). The rationale was that the dichotomous classification of fluoridation (<75% or ≥75%) provides an estimate of the association at a pragmatic public health level, recognizing that many counties have some fraction of the population that does not use a public water system, making 100% fluoridation unattainable. In contrast, the continuous measure of fluoridation estimates the likely impact of fluoridation in a situations where 100% coverage is attainable.

For primary dentition caries, mean dfs was 4.6 in counties with <75% fluoridation compared to 3.3 in counties with ≥75% fluoridation and the covariate-adjusted group difference between the two groups was 1.39 (i.e., after adjusting for socio-demographics and dental behaviors). Using the continuous measure of county-level fluoridation, the adjusted difference associated with 0% versus 100% fluoridation was 2.1. In the permanent dentition, mean DMFS was 2.2 and 1.9 in <75% fluoridation and ≥75% fluoridation counties, the fully-adjusted difference was 0.25, while, using continuous measure of fluoridation, the difference between 0% versus 100% fluoridation was 0.88. However, it is more informative to consider those effect estimates for groups of children, rather than for individuals. To that end, Table 3 summarizes the same effect estimates for an average group of 30 children in the U.S. population (i.e., the approximate number of children in a school classroom). Based on the contrast of 0% with 100%, fluoridation is associated with 62 fewer cavities in primary teeth per thirty 2-8 year olds, and 26 fewer cavities in permanent teeth per thirty 6-17 year olds (Table 3).

Table 3: Caries experience expressed as number of affected tooth surfaces per 30 children in the U.S. child and adolescent population*

Age-group, caries index	Observed means in counties with <75% fluoridation	Observed means in counties with ≥75% fluoridation	Covariate-adjusted mean difference <75% vs. ≥75% fluoridation	Covariate-adjusted mean difference 0% vs. 100% fluoridation
2-8 yr olds, dfs per 30 children	138	100	42	62
6-17 yr olds, DMFS per 30 children	66	57	7	26

* Based on observed means reported in Table 4 and regression-model adjusted differences reported in Table 5 of Slade et al. [49]



Reduction: <75% vs. ≥75%	Income to poverty ratio 0.5	1	2	3	4
Absolute	2.0	1.8	1.3	0.9	0.4
Relative	30%	29%	26%	22%	15%

Figure 1: Income-gradients in dental caries of U.S. children are attenuated by fluoridation. [50]

The second publication from the same study investigated income-associated inequality in dental caries experience, comparing counties where <75% of the population was served by fluoridated water with counties where ≥75% of the population was served by fluoridated water. In the primary dentition, there was a statistically significant interaction between county-coverage of fluoridation and household income. The interaction provided statistical evidence that the income-gradient in dental caries was attenuated by 41% in predominantly fluoridated counties compared to communities with <75% fluoridation (i.e., gradients of -1.06 and -0.62, respectively; see Figure 1). In the permanent dentition, the gradient was also attenuated, but not to a statistically significant degree.

As such, fluoride in drinking water represents a rare preventive intervention that is associated with greater preventive benefits in low-income groups than in high-income groups.

In addition to the original studies reported in Table 2, there have been two systematic reviews reported since the 2015 Cochrane systematic review (Table 4).

Table 4: Systematic reviews reported since the 2015 Cochrane systematic review

Year(s) and setting for data collection	Methods (row 1) Results (row 2)
2016, Australia, Evidence evaluation of fluoridation and dental caries [55]	Review of previous systematic reviews (through 2015) and subsequently-published association studies through 2016 (n=15 studies of primary dentition caries; n=21 studies of permanent dentition) by the Fluoride Reference Group of the Australian National Health and Medical Research Council.
	Main conclusions: • "water fluoridation reduces tooth decay by 26-44% in children, teenagers and adults". • "there is consistent evidence that water fluoridation reduces tooth decay for all socio-economic groups" • "there is some additional evidence that suggests water fluoridation reduces inequality in tooth decay experienced by those in lower socio-economic groups and those living in regional areas.
2016, Canada, Systematic review of fluoridation cessation [56]	Systematic review of n=15 studies that investigated caries experience before- and after-cessation of community water fluoridation.
	Of 9 studies that met criteria for methodological quality, five showed an increase in caries after cessation of fluoridation, 3 studies did not show an increase, and one could not be adjudicated.

2.3.6. Critical appraisal of studies reported since the 2015 Cochrane systematic review

In each instance of primary studies reported since 2015 (Table 2), the study designs were of the type that did not meet the criteria for study selection in the 2015 Cochrane review. That is, the subsequently reported studies either used a cross-sectional design or sequential cross-sectional surveys before and after fluoridation (or defluoridation), but with no comparison community. Hence, if a systematic review were to be repeated today using the same study selection criteria as applied for the Cochrane review,[43] none of the new studies would be included. Yet, other systematic reviews conducted since 2015 were more inclusive in their selection criteria than the 2015 Cochrane systematic review. In each instance, those other systematic reviews evaluated a considerably larger body of evidence, and they were more affirmative in concluding that fluoridation was associated with lower levels of dental caries than was the 2015 Cochrane systematic review. Specifically, the Australian evidence review considered cross-sectional studies excluded by the 2015 Cochrane systematic review, along with 26 studies published since the 2015 Cochrane systematic review, concluding that fluoridation reduces tooth decay by 26-44% (a higher upper bound than the 26-35% reported in the 2015 Cochrane systematic review). The Australian review was also more affirmative with respect to effects of fluoridation on socio-economic inequalities in dental caries. Likewise, the systematic review of fluoridation cessation,[56] in concluding that "overall, the published research points more to an increase in dental caries post-CWF [community water fluoridation] cessation than otherwise", was more assertive than the 2015 Cochrane systematic review which concluded "there is insufficient information to determine the effect of stopping water fluoridation programmes on caries levels".

In summary, studies reported since 2015 continue to show dental caries preventive benefits associated with exposure to fluoridated drinking water. The two new systematic reviews used more inclusive selection criteria than the 2015 Cochrane systematic review and were more affirmative in their conclusions of a caries-preventive benefit.

2.3.7. Epidemiologic studies of water fluoridation and dental caries in adults

Epidemiologic studies in adults of the association between water fluoridation and dental caries date back to 1948[57] when a markedly lower-than expected rate of dental decay and tooth extraction was seen in adults who were lifetime residents of Colorado Springs, CO, where drinking water contained 2.6 mg/L F. When later compared with lifetime resident of non-fluoridated Bolder, CO, [58] the rates in Colorado Springs were approximately 60 percent lower. Ironically, those two studies were not included in a 2007 systematic review of the fluoridation and dental caries in adults because the search was limited to studies published since 1966. Instead, that 2007 systematic review[59] used results from nine published studies: one was a prospective cohort study, one was a an ecological study, and seven were cross-sectional studies of adults who were lifetime residents of either fluoridated or non-fluoridated areas. Pooled results from meta-analysis revealed a reduction of one third (34.6%, 95%CL: 12.6%, 51.0%) in caries experience associated with lifetime exposure to approximately 1mg/L F (range 0.7 to 2.0 mg/L F).

Since that systematic review, six cross-sectional studies of adults have investigated the relationship, as summarized in Table 5. The one U.S. study during that period investigated tooth loss, not total caries experience, using a nationally-representative sample of adults.

Table 5: Studies published since 2007 examination associations between fluoridation and dental caries experience in Adults

Year(s) and setting for data collection	Methods (row 1) Results (row 2)
2006 Australia, DMFT of 17-56 yr olds [16]	Cross-sectional clinical and radiographic examination survey of n=876 armed forces recruits. Fluoridation status of each residential location was determined from a national database of fluoridation history of public water supplies.
	Mean DMFT in recruits with ≥50% lifetime exposure was 24% lower than recruits with the <10% lifetime exposure group.
2008, Australia, DMFT of 17-35 yr olds[17]	Cross-sectional clinical and radiographic examination survey of n=1084 army recruits. A questionnaire asked about socio-demographic characteristics and residential locations throughout life. Fluoridation status of each residential location was determined from a national database of fluoridation history of public water supplies.
	Mean DMFT in recruits with lifetime exposure to fluoridated drinking water was 3.02 compared to 3.87 for recruits with no exposure.
1992-1999, U.S. missing teeth of 23-49 yr olds[18]	Cross-sectional telephone interview survey with 81,337 adults in the Behavioral Risk Factor Surveillance System Survey, where tooth loss due to dental disease was reported in four categories. The 1992 Fluoridation Census was used to calculate each respondents county-of-residence at the time of the survey, 20 years earlier, and at birth.
	Lower levels of tooth loss were significantly associated with residence in fluoridated counties at the time of the respondent's birth, but not to fluoridation at the time of the survey.
2004-06, Australia, DMFT and DFS of 18->65 yr olds[19]	Cross-sectional dental examination survey of a nationally representative sample of n=3,779 adults who also completed a questionnaire asking about socio-demographic characteristics and residential locations throughout life. Fluoridation status of each residential location was determined from a national database of fluoridation history of public water supplies.
	After adjustment for sociodemographic characteristics, adults with >75% of lifetime exposure to fluoridation had 10% fewer DMFT compared to adults with < 25% of lifetime exposure. The percentage difference was similar for people who were exposed to fluoridation before- and after birth, and for people exposed only after birth.
2012, Brazil, DMFT of 20-59 yr olds[20]	Cross-sectional dental examination survey of n= 1,140 people born in Florianópolis where fluoridation was implemented in 1982 and 1986 in different parts of the city. Questionnaires asked about residential locations throughout life.
	Relative to people with access to fluoridated water for >75% of their lifetime, DMFT was greater for people with 50%-75% lifetime exposure (ratio=1.34) and for people with <50% lifetime exposure (ratio=1.34)
2006-2011, Australia, DMFS in 20-35 yr olds[21]	Cross-sectional dental examination survey of n=1,221 people in South Australia who had first participated in a 1991-1992 survey. Questionnaire asking about socio-demographic characteristics and residential locations throughout life were administered and percentage of lifetime with access to fluoridation was determined from a national database of fluoridation history of public water supplies.
	Relative to people with 100% lifetime exposure to fluoridation, people with <75% lifetime exposure had greater DMFS (ratio=1.26). Relative effects were of a similar when fluoridation exposure was calculated separately as percentage of childhood exposed and percentage of adolescence/adulthood exposed.

2.3.8. Critical appraisal of studies of water fluoridation and dental caries in adults

Overall, findings from studies of adults corroborate results from studies of children: exposure to water fluoridation is associated with lower levels of dental caries experience. There is also some indication that the magnitude of preventive benefit was greater in historical studies. For example, the 2007 systematic review[59] of studies reported since 1966 estimated an overall relative difference of one third, whereas most of the subsequent studies summarized in Table 5 report smaller relative differences. Also, as seen in studies of children, the systematic review in adults[59] used more inclusive selection criteria than the 2015 Cochrane systematic review which also included studies of adults, but which concluded that "no studies that aimed to determine the effectiveness of water fluoridation for preventing caries in adults met the review's inclusion criteria".[43]

Some studies of adults distinguish between preventive benefits from exposure in childhood and in adulthood, suggesting that both periods of exposure are important. Consistently, though, the studies reviewed in Table 5 conclude that lifetime exposure to fluoridation confers the greatest caries-preventive benefit. This finding is considered in further detail in the next section, which reviews hypothesized biological mechanisms underlying the preventive benefits observed in association studies.

2.3.9. Causal inference and biological mechanisms of action

There are well-established criteria to evaluate whether or not an association between exposure and disease is causal. For example, when judging the health effects of smoking (which, on ethical grounds, can never be tested in an experimental study of humans), the 2004 U.S. Surgeon General's Report[60] applied seven criteria. Those criteria as they apply to caries-preventive benefits of water fluoridation are reviewed briefly below.

1. *Consistency: results from association studies should be replicated in different studies and populations.*
   As reviewed above, systematic reviews from studies spanning more than half a century and conducted in multiple countries are consistent in concluding that exposure to water fluoridation is associated with lower levels of dental caries in children.
2. *Strength of association: a greater magnitude of effect suggests an association that is more likely causal.*
   The first association studies, conducted at a time when dental caries was rampant, and when fluoride was available only in drinking water demonstrated profound reductions in dental caries experience associated with lifetime exposure to fluoridation.
3. *Specificity*[*]*: the exposure should be associated with only one or a few diseases.*
   While fluoridation has been investigated for potential preventive effects in other oral diseases (including gingivitis and periodontal disease), no association was found.
4. *Temporality: exposure to the putative cause should precede development of the disease.*
   As noted in above, this criterion is satisfied in studies that measure lifetime caries experience in lifetime residents of either fluoridated or non-fluoridated areas.
5. *Biological gradient: incremental effects on disease are observed with incrementally greater exposure*
   This was demonstrated first in Dean's "21-cities" study,[32] where the concentration of fluoride varied, and has been verified in later studies that expressed the degree of exposure as a percentage of lifetime living in places fluoridated at around 1 mg/L F (see Section 2.3.3)
6. *Experiment: studies of natural variation that plausibly imitate conditions of a randomized experiment.*
   This criterion was addressed most convincingly in the five "twin-cities" trials (Section 2.3.2) where intervention and control cities were studied in parallel, over multiple years, making them equivalent to experimental trials in many aspects, although not with respect to random allocation. Subsequent studies with comparable, non-

[*] The Surgeon General's report gives least credence to the specificity criterion when evaluating chronic diseases, noting that its existence can strengthen a causal claim, but its absence does not weaken it.

randomized designs were reviewed and given the highest quality ratings in systematic reviews reported this century.

7. *Coherence, plausibility and analogy: a proposed causal relationship should not violate known scientific principles.* The causal interpretation is *biologically plausible*, with good evidence that dental caries prevention is due to a combination of pre-eruptive mechanisms (i.e., incorporation of fluoride into developing enamel which becomes more resistant to subsequent acid attacks) and post-eruptive mechanisms (i.e., concentration of intra-oral fluoride in dental biofilm, inhibiting demineralization and enhancing remineralization).

3. Author's signature

Gary Slade Digitally signed by Gary Slade
DN: cn=Gary Slade, o, ou, email=gary_slade@dentistry.unc.edu, c=US
Date: 2020.02.03 15:26:32 -05'00'

Gary D. Slade, BDSc, DDPH, PhD

John W. Stamm Distinguished Professor of Dentistry, Division of Pediatric and Public Health, UNC Adams School of Dentistry, Koury Oral Health Sciences Room 4501E, 385 South Columbia Street, Chapel Hill, NC 27599

Phone: [Int +1] 919-537-3273. Email: gary_slade@unc.edu

4. Bibliography and cited references

1. Fejerskov O. Changing paradigms in concepts on dental caries: consequences for oral health care. Caries Res. 2004;38(3):182-91.
2. Whitford GM, Thomas JE, Adair SM. Fluoride in whole saliva, parotid ductal saliva and plasma in children. Arch Oral Biol. 1999;44(10):785-8.
3. Buzalaf MA, Levy SM. Fluoride intake of children: considerations for dental caries and dental fluorosis. Monogr Oral Sci. 2011;22:1-19.
4. Burt BA, Eklund SA, Ismail AI. Fluoride: Human Health and Caries Prevention. Chapter 23 in: Dentistry, dental practice, and the community. 5th Ed. 5th ed. Philadelphia: Saunders; 1999.
5. Arnold FAJ. The use of fluoride compounds for the prevention of dental caries. Int Dent J. 1957;7:54-72.
6. Schamschula RG, Agus H, Charlton G, Duppenthaler JL, Un P. Associations between fluoride concentration in successive layers of human enamel and individual dental caries experience. Arch Oral Biol. 1979;24(10-11):847-52.
7. DePaola PF, Brudevold F, Aasenden R, Moreno EC, Englander H, Bakhos Y, Bookstein F, Warram J. A pilot study of the relationship between caries experience and surface enamel fluoride in man. Arch Oral Biol. 1975;20(12):859-64.
8. Fejerskov O, Thylstrup A, Larsen MJ. Rational use of fluorides in caries prevention. A concept based on possible cariostatic mechanisms. Acta Odontol Scand. 1981;39(4):241-9.

9. Groeneveld A, Van Eck AA, Backer Dirks O. Fluoride in caries prevention: is the effect pre- or post-eruptive? J Dent Res. 1990;69 Spec No:751-5; discussion 820-3.

10. Dirks OB. The benefits of water fluoridation. Caries Res. 1974;8(0):suppl:2-15.

11. Featherstone JD. Prevention and reversal of dental caries: role of low level fluoride. Community Dent Oral Epidemiol. 1999;27(1):31-40.

12. Lauris JR, da Silva Bastos R, de Magalhaes Bastos JR. Decline in dental caries among 12-year-old children in Brazil, 1980-2005. Int Dent J. 2012;62(6):308-14.

13. Koh R, Pukallus ML, Newman B, Foley M, Walsh LJ, Seow WK. Effects of water fluoridation on caries experience in the primary dentition in a high caries risk community in Queensland, Australia. Caries Res. 2015;49(2):184-91.

14. Johnson NW, Lalloo R, Kroon J, Fernando S, Tut O. Effectiveness of water fluoridation in caries reduction in a remote Indigenous community in Far North Queensland. Aust Dent J. 2014;59(3):366-71.

15. McLaren L, Patterson S, Thawer S, Faris P, McNeil D, Potestio ML, Shwart L. Exploring the short-term impact of community water fluoridation cessation on children's dental caries: a natural experiment in Alberta, Canada. Public Health. 2017;146:56-64.

16. Mahoney G, Slade GD, Kitchener S, Barnett A. Lifetime fluoridation exposure and dental caries experience in a military population. Community Dent Oral Epidemiol. 2008;36(6):485-92.

17. Hopcraft MS, Yapp KE, Mahoney G, Morgan MV. Dental caries experience in young Australian Army recruits 2008. Aust Dent J. 2009;54(4):316-22.

18. Neidell M, Herzog K, Glied S. The association between community water fluoridation and adult tooth loss. Am J Public Health. 2010;100(10):1980-5. PMCID: PMC2936985.

19. Slade GD, Sanders AE, Do L, Roberts-Thomson K, Spencer AJ. Effects of fluoridated drinking water on dental caries in Australian adults. J Dent Res. 2013;92(4):376-82.

20. Peres MA, Peres KG, Barbato PR, Hofelmann DA. Access to Fluoridated Water and Adult Dental Caries: A Natural Experiment. J Dent Res. 2016;95(8):868-74.

21. Spencer AJ, Liu P, Armfield JM, Do LG. Preventive benefit of access to fluoridated water for young adults. J Public Health Dent. 2017;77(3):263-71.

22. Singh KA, Spencer AJ. Relative effects of pre- and post-eruption water fluoride on caries experience by surface type of permanent first molars. Community Dent Oral Epidemiol. 2004;32(6):435-46.

23. Singh KA, Spencer AJ, Armfield JM. Relative effects of pre- and posteruption water fluoride on caries experience of permanent first molars. J Public Health Dent. 2003;63(1):11-9.

24. Singh KA, Spencer AJ, Brennan DS. Effects of water fluoride exposure at crown completion and maturation on caries of permanent first molars. Caries Res. 2007;41(1):34-42.

25. Slade GD, Davies MJ, Spencer AJ, Stewart JF. Associations between exposure to fluoridated drinking water and dental caries experience among children in two Australian states. J Public Health Dent. 1995;55(4):218-28.

26. Cho HJ, Jin BH, Park DY, Jung SH, Lee HS, Paik DI, Bae KH. Systemic effect of water fluoridation on dental caries prevalence. Community Dent Oral Epidemiol. 2014;42(4):341-8.

27. Tubert-Jeannin S, Auclair C, Amsallem E, Tramini P, Gerbaud L, Ruffieux C, Schulte AG, Koch MJ, Rege-Walther M, Ismail A. Fluoride supplements (tablets, drops, lozenges or chewing gums) for preventing dental caries in children. Cochrane Database Syst Rev. 2011(12):CD007592.

28. Yeung CA, Chong LY, Glenny AM. Fluoridated milk for preventing dental caries. Cochrane Database Syst Rev. 2015(9):CD003876.

29. Marino R, Traub F, Lekfuangfu P, Niyomsilp K. Cost-effectiveness analysis of a school-based dental caries prevention program using fluoridated milk in Bangkok, Thailand. BMC Oral Health. 2018;18(1):24. PMCID: PMC5815217.

30. Banoczy J, Rugg-Gunn A, Woodward M. Milk fluoridation for the prevention of dental caries. Acta Med Acad. 2013;42(2):156-67.

31. Dean HT. Endemic fluorosis and its relation to dental caries. Public Health Reports. 1938;53:1443-52. PMCID: PMC2110810.

32. Dean HT, Arnold FAJ, Elvove E. Domestic water supplies and dental caries. V. Additional studies on the relation of fluoride domestic waters to dental caries experience in 4,425 white children, aged 12 to 14 years, of 13 cities in 4 states. Public Health Reports. 1942;57:1155-79. PMCID: PMC1968063.

33. Dean HT, Arnold FA, Jr., Jay P, Knutson JW. Studies on mass control of dental caries through fluoridation of the public water supply. Public Health Rep. 1950;65(43):1403-8.

34. Arnold FA, Jr., Dean HT, Jay P, Knutson JW. Effect of fluoridated public water supplies on dental caries prevalence. Public Health Rep. 1956;71(7):652-8. PMCID: PMC2031043.

35. Backer Dirks O, Houwink B, Kwant GW. The results of 6 1/2 years of artificial fluoridation of drinking water in the Netherlands. The Tiel-Culemborg experiment. Arch Oral Biol. 1961;5:284-300.

36. Ast DB, Fitzgerald B. Effectiveness of water fluoridation. J Am Dent Assoc. 1962;65:581-7.

37. National Health and Medical Research Council. The effectiveness of water fluoridation. In: NHMRC, editor. Canberra: Commonwealth of Australia; 1991.

38. United States. Public Health Service., Okun DA. Public Health Service drinking water standards. Rev. 1962. ed. Washington: U.S. Dept. of Health, Education, and Welfare, Public Health Service; 1962.

39. Centers for Disease Control and Prevention. National Fluoridation Statistics.; [cited April 26, 2018]; Available from: https://www.cdc.gov/fluoridation/statistics/FSGrowth.htm.

40. Murray JJ, Rugg-Gunn AJ, Jenkins GN. Fluorides in caries prevention. 3rd ed. Oxford ; Boston: Butterworth-Heinemann; 1991.

41. Newbrun E. Effectiveness of water fluoridation. J Public Health Dent. 1989;49(5 Spec No):279-89.

42. Rugg-Gunn AJ, Do L. Effectiveness of water fluoridation in caries prevention. Community Dentistry and Oral Epidemiology. 2012:40 Suppl 2: 55-64.

43. Iheozor-Ejiofor Z, Worthington HV, Walsh T, O'Malley L, Clarkson JE, Macey R, Alam R, Tugwell P, Welch V, Glenny AM. Water fluoridation for the prevention of dental caries. Cochrane Database Syst Rev. 2015:Issue 6. Art. No.: CD010856.

44. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, Atkins D, Methods Work Group TUSPSTF. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001;20(3 Suppl):21-35.

45. McDonagh MS, Whiting PF, Wilson PM, Sutton AJ, Chestnutt I, Cooper J, Misso K, Bradley M, Treasure E, Kleijnen J. Systematic review of water fluoridation. BMJ. 2000;321(7265):855-9. PMCID: 27492.

46. National Health and Medical Research Council. A systematic review of the efficacy and safety of fluoridationpart a: review of methodology and results. Australian Government; 2007.

47. Community Preventive Services Taskforce. Oral Health: Preventing Dental Caries, Community Water Fluoridation. 2013 [updated 2013; cited December 28. 2018]; Available from: https://www.thecommunityguide.org/sites/default/files/assets/Oral-Health-Caries-Community-Water-Fluoridation_3.pdf.

48. Parnell C, Whelton H, O'Mullane D. Water fluoridation. Eur Arch Paediatr Dent. 2009;10(3):141-8.

49. Slade GD, Grider WB, Maas WR, Sanders AE. Water Fluoridation and Dental Caries in U.S. Children and Adolescents. J Dent Res. 2018;97(10):1122-8. PMCID: PMC6169031.

50. Sanders AE, Grider WB, Maas WR, Curiel JA, Slade GD. Association Between Water Fluoridation and Income-Related Dental Caries of US Children and Adolescents. JAMA Pediatr. 2019;173(3):288-90. PMCID: PMC6439886.

51. Blinkhorn AS, Byun R, Mehta P, Kay M. A 4-year assessment of a new water-fluoridation scheme in New South Wales, Australia. Int Dent J. 2015;65(3):156-63.

52. Crouchley K, Trevithick R. Dental Health Outcomes of Children Residing in Fluoridated and Non-Fluoridated Areas in Western Australia. In: Department of Health WA, editor. Perth, Australia2016.

53. Do LG, Ha DH, Roberts-Thomson KF, Jamieson L, Peres MA, Spencer AJ. Race- and Income-Related Inequalities in Oral Health in Australian Children by Fluoridation Status. JDR Clinical and Translational Research. 2018;3(2):170-9.

54. Water fluoridation. Health monitoring report for England 2014. In: England PH, editor. London: Crown copyright; 2014.

55. National Health and Medical Research Council. Information paper – Water fluoridation: dental and other human health outcomes, report prepared by the Clinical Trials Centre at University of Sydney. In: NHMRC, editor. Canberra: Commonwealth of Australia; 2017.

56. McLaren L, Singhal S. Does cessation of community water fluoridation lead to an increase in tooth decay? A systematic review of published studies. J Epidemiol Community Health. 2016;70(9):934-40. PMCID: PMC5013153.

57. McKay FS. Mass control of dental caries through the use of domestic water supplies containing fluorine. Am J Public Health Nations Health. 1948;38(6):828-32. PMCID: PMC1624454.

58. Russell AL, Elvove E. Domestic water and dental caries. VII. A study of the fluoride-dental caries relationship in an adult population. Public Health Rep. 1951;66(43):1389-401.

59. Griffin SO, Regnier E, Griffin PM, Huntley V. Effectiveness of fluoride in preventing caries in adults. Journal of dental research. 2007;86(5):410-5.

60. U.S. Surgeon General. The Health Consequences of Smoking: A Report of the Surgeon General. Atlanta (GA)2004.