Water Fluoridation

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Contents

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Learning Objectives

- Define water fluoridation.
- List the types of studies in their chronological sequence along the path to building the evidence on the effectiveness of water fluoridation.
- Compare the effect size of reduction in caries across studies by time and study design.
- What are the potential sources of bias in studies on water fluoridation?
- Differentiate the ways in which exposure has been measured in studies of water fluoridation.
- How can measurement of caries outcomes bias study findings?

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29.1 Introduction

Oral epidemiology has played a central role in documenting the burden of oral disease, describing the natural history, establishing the risk of occurrence, investigating success in managing disease, and finally establishing paths for disease prevention. As dental caries is frequently described as the most common childhood noncommunicable disease and has the most substantial burden of illness among all oral diseases, it is not surprising that oral epidemiology has focused greatly on dental caries. Fortunately, oral epidemiology has contributed to the great progress in understanding the etiology and the opportunities for prevention of caries.

The use of fluorides, at a population level and individually, has been crucial to approaches to caries prevention. Fluorides have transformed oral health over the last 75 years. While fluoride does not vaccinate against caries, it has reduced the burden of caries by a staggering degree. What was once unmanageable by clinical restorative interventions has now become more manageable by the dental healthcare system in many countries. At the population-level fluoridation of drinking water, salt or milk has been the cornerstone for caries prevention. The widespread behavior of tooth brushing has also created an opportunity for caries prevention with fluoridated toothpaste. Together fluoridation and fluoridated toothpaste are credited with much of the decline in the burden of caries.

The evolution of fluoride as the central agent in caries prevention began with water fluoridation. Water fluoridation is the adjustment of the level of fluoride in a drinking water supply to achieve near maximal prevention of caries without the occurrence of dental fluorosis of public health or aesthetic concern. Water fluoridation has been acknowledged as one of the great public health measures of the twentieth century [1]. All formal reviews, whether systematic or narrative reviews, have concluded that water fluoridation is effective in reducing the prevalence and severity of dental caries in children and adolescents and increasingly young adults and adults.

29.2 Evolution of the Oral Epidemiological Evidence

The development of the theory and subsequently the evidence around the benefit of fluoridated drinking water followed a path of clinical cases, observation in a natural experiment, through to clinical trials, and then public health monitoring. In many respects this is a "classic" story within epidemiology. The following description of the evolution of the oral epidemiological evidence draws heavily on work by Whelton et al. [2]

From late in the nineteenth century, there was reference to the phenomenon of mottled enamel, enamel opacities which might take on staining and loss or pitting of the tooth enamel in its more severe form. McKay in 1916 [3] is credited with observing that children with mottled enamel, although their teeth seemed structurally imperfect, were less susceptible to dental caries. McKay [3] suspected that these outcomes were the result of something in drinking water but did not know what. The answer to what was in the drinking water, fluoride, came from Churchill in 1931 and was dependent on development of scientific instrumentation to measure low levels of fluoride in drinking water [4].

Initially the focus was on fluoride and mottled enamel. Dean and colleagues set about observing the prevalence and severity of mottled enamel across many communities in the USA. Dean developed a specific index, Dean's Index of Dental Fluorosis [5], and determined the dose-response relationship between naturally occurring fluoride in drinking water and the prevalence and distribution of dental fluorosis in communities. This observational research was conducted across some 22 communities [6, 7]. In the meantime, Ainsworth [8] had added to the reports that dental caries was lower in a community with a high fluoride level in drinking water. Interest grew in broadening the dose-response observational studies to consider both dental caries and dental fluorosis as outcomes. Bodecker and Bodecker [9] had developed measures for dental caries in individuals, and Dean and others applied these measures to early teenage children, 12–14 years old, in 21 communities mostly in Illinois and Texas in the USA [10, 11]. The "21 cities" study provided the dose-response evidence that generated the hypothesis that at around 1 mg F/L, there was near maximal prevention of dental caries without dental fluorosis of public health concern [12] (Fig. 29.1).

The benefit or harm of fluoride in drinking water was specified across populations with differing levels of naturally occurring fluoride in drinking water. The anal-

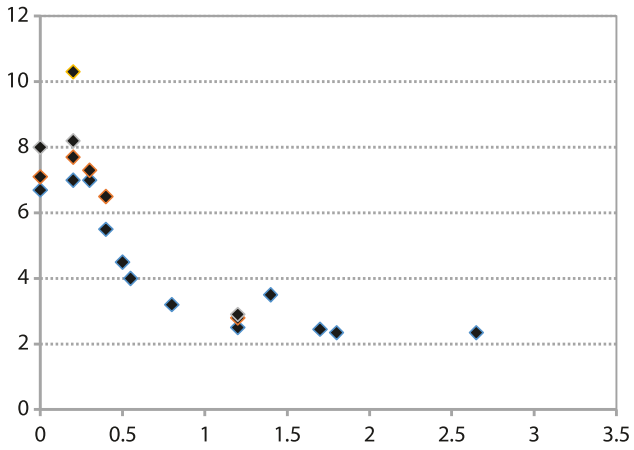

Fig. 29.1 Dose-response relationship between fluoride in a water supply and caries experience (DMFT) from Dean's 21 cities study [12]

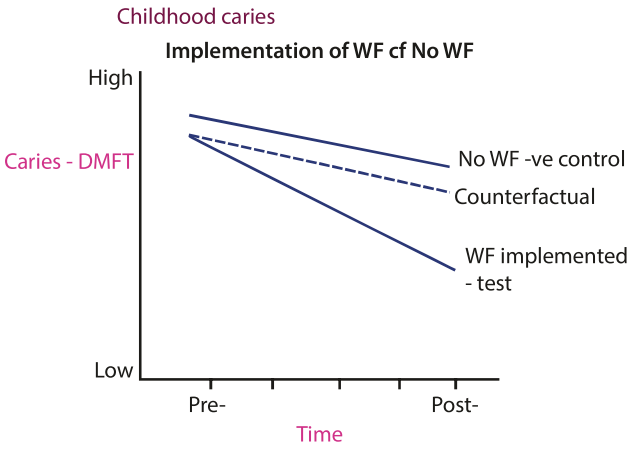

Fig. 29.2 Before and after non-randomized controlled study comparing non-fluoridated (No WF -ve control) to fluoridated (WF implemented- test) sites and the counterfactual

ysis focused on group differences not differences within a group [13]. It sought to find populations that had a low prevalence and experience of dental caries and a low prevalence of dental fluorosis.

A hypothesis emerged out of the dose-response data that the fluoride level in water supplies which had negligible fluoride could be adjusted upward to achieve a near maximal prevention of caries without endemic dental fluorosis of concern. This was articulated by Ast in 1943, and Dean in 1944 outlined the community fluoridation trials that would soon follow [12, 14]. Research entered a phase of foundational community fluoridation trials.

Community fluoridation trials were conducted as before and after non-randomized controlled studies. These are an attempt to mimic an experimental design using observational data, studying the differential effect of an intervention. They assess the effect of water fluoridation on caries in an intervention group by comparing the change over time in both the intervention and control groups. Such studies are prospective, comparing groups over time.

Some assumptions are involved in the comparisons usually stated as the counterfactuals: the preexisting or before differences are assumed to be fixed over time; and difference in the differences across time is assumed to be a causal effect (Fig. 29.2).

Three Trials were Commenced in the USA and One in Canada

- Grand Rapids (1945), Michigan, paired with nearby Muskegon and the naturally fluoridated Aurora, Illinois (1.2 mg F/L), as a positive control
- Newburgh (1945), New York, paired with Kingston, New York
- Evanston (1946), Illinois, paired with Oak Park, Illinois
- Brantford (1945), Ontario, paired with Sarnia, Ontario, and the naturally fluoridated Stratford, Ontario, as a positive control

The first findings from the Grand Rapids trial were released in 1950 [15]. These findings included the baseline and the 4-year follow-up data. This created a difficulty. The control site quickly became aware of the early findings of positive reductions in caries in the fluoridation site and sought to implement fluoridation. Muskegon fluoridated in mid-1951, eliminating the paired negative control. This contributed to the complexity of the way findings were reported for the Grand Rapids trial as it progressed. Many findings are presented as before and after comparisons in the trial site, something which becomes important in including/excluding this in evidence in later systematic reviews of the effectiveness of water fluoridation.

The findings in the USA and Canada spurred interest from other counties, and the research entered a replication phase. There are two aspects to the replication phase. First, the dose-response relationship between fluoride occurring naturally is a water supply, and caries experience was replicated in the USA and further countries in the late 1940s and through the 1950s [16]. The curvilinear relationship was confirmed and around 1.0 mg F/L was supported as the level at which near maximal reduction in caries experience was achieved in children. Second, water fluoridation was initiated in Australia, Belgium, Brazil, Canada, Chile, Colombia, El Salvador, Germany, Great Britain, Japan, Malaysia, the Netherlands, New Zealand, Panama, Sweden, and Venezuela [17]. Some countries initiated trials similar to the first wave of studies in the USA and Canada, notably the Tiel-Culemborg study in The Netherlands initiated in 1953 [18]; a study in Hastings, New Zealand,

initiated in 1954 [19]; and Watford, Kilmarnock, and part of Anglesey in the UK initiated in 1955–1956, with Sutton, Ayr, and the remaining part of Anglesey acting as control towns [20]. These further trials built up the body of evidence for the effectiveness of fluoridating drinking water for the prevention of caries in children and adolescents.

Over time fewer sites conducted trials. After all, the effectiveness of water fluoridation had been endorsed by the US Public Health Service in 1952, accepted by the WHO in 1958, and recommended with specific accommodation of varying climatic conditions by the US Health and Human Services in 1962. Further as population coverage by water fluoridation increased and then stabilized, there were fewer opportunities to conduct before and after non-randomized controlled studies. In theory other study designs could have been pursued that are at a similar level in the strength of evidence. These include cohort studies, case-control studies, and interrupted time series with a control group. These study types share a characteristic of attempting to establish time precedence of the exposure before the observation of the outcome in the intervention group in comparison to the control group. However, they have been rarely used in research around water fluoridation.

Attention turned to demonstration studies to establish the feasibility and applicability of water fluoridation in different environments, especially after the mid-1960s. Public health authorities desired information on whether water fluoridation was providing a benefit for their community of concern [21]. Two study designs were employed: ecological studies and cross-sectional concurrent controlled studies. In many circumstances these designs cannot establish the time precedence that exposure preceded the development of the disease outcome. However, Slade et al. [22] have pointed out that the temporal ordering between exposure and disease is still informed when studies compare lifetime exposure and non-exposure and when disease is quantified as lifetime, cumulative incidence, i.e., the DMFT measure in a study of dental caries. The ecological and cross-sectional studies vary in how the exposure is defined: ecological studies classify exposure of a group sharing an environment such as residence in a fluoridated area, whereas cross-sectional studies classify exposure at an individual level. While these observational study designs are regarded as lower in the evidence hierarchy, modern epidemiology and computing power has generated new analytic approaches that have added considerable confidence to the reduction of the risk of bias in these studies.

The path from clinical observation to a widely practiced public health measure of accepted benefit to the community has been long and involved studies of different design and quality. A notable feature is the consistency with which research along the pathway over 70 years has documented a benefit in prevention of caries associated with water fluoridation. Consistency across settings and study designs was identified as an important and useful criterion in evaluating and grading evidence in public health [23]. Together the evidence across this research has been sufficient for water fluoridation to be recognized as a great public health achievement.

29.3 Findings from Across Clinical Trials to Monitoring Studies

Early research on water fluoridation supported reductions of 45–60% in caries severity against control groups. In the Newburgh-Kingston trial, a consistent reduction in caries among children in the fluoridated town was found compared to the non-fluoridated town over an extended period. After 10 years the reductions in caries (DMFT) among 6–9-, 10–12-, and 13–14-year-old children ranged from 57 to 48%. The reduction in 16-year-old children was lower at 41% [24]. In the Evanston-Oak Park trial, caries in 12–14-year-old children in the fluoridated town decreased by 57% to 49% compared to the non-fluoridated town [25].

Two systematic reviews of the evidence from the before and after non-randomized controlled trials conducted in either the first wave of trials or the replication phase support the substantial difference in caries severity that emerged after the implementation of water fluoridation [26, 27]. Both systematic reviews ended up focused on dental caries in children. Both reviews included studies across a wide time span. For instance, Iheozor-Ejiofor et al. [27] review included studies from 1951 to 1984 and one more recent 2012 unpublished study.

The Iheozor-Ejiofor et al. [27] review included studies that reported on different ages of children and measures of caries. They estimated the pooled effect of water fluoridation on caries and examined the heterogeneity of the effect. The key findings are summarized in Table 29.1.

Iheozor-Ejiofor et al. [27] concluded that there were few recent studies meeting the review's inclusion criteria. Most of the available data came from studies conducted prior to 1975.This is consistent with the path that has been pursued in developing and then monitoring water fluoridation as a public health measure. There was a consistency in the direction of the findings across the studies, but there was heterogeneity in the size of the effect. This was evident across ages of children, caries measures, and time at which the study was conducted.

Table 29.1 Summary of the reductions in caries in children in before and after non-randomized controlled studies with different outcome measures from the systematic review by Iheozor-Ejiofor et al. [27] (2015)

Measure	No. of studies	Findings
2015 Iheozor-Ejiofor et al. review		**Before and after non-randomized controlled trials**
dmft	9	35% mean reduction with fluoridation 1.81 tooth reduction (95% CI 1.31–2.31)
DMFT	10	26% mean reduction with fluoridation 1.16 tooth reduction (95% CI 0.72–1.61)
% dmft = 0	10	15% mean increase with fluoridation (95% CI 11–19%)
% DMFT = 0	8	14% mean increase with fluoridation (95% CI 5–23%)

After NHMRC 2017 [28]

Estimates of the effect size for differences in caries in children also exist for studies out of the monitoring phase. The table below summarizes the findings of studies from a review of cross-sectional concurrent controlled studies [29]. Many studies were included. Table 29.2 presents the median reduction and the range from the individual studies. Table 29.2 also includes an individual study with a different study design, a multilevel ecological study [30]. The effect size of this multilevel ecological study was a 37–39% reduction in caries experience in fluoridated areas. The effect sizes of all the studies in Table 29.2 are not dissimilar to that observed for the before and after non-randomized controlled studies included in the Iheozor-Ejiofor et al. review [27].

One message from Table 29.1 and 2 is that the body of research on the effectiveness of water fluoridation consistently supports its benefit. This holds across different designs. However, the effect size in individual studies varies within studies of the same design and across studies of a different design. What is it in the methods of oral epidemiology applied to research on the effectiveness of water fluoridation that helps us understand this variation, and which should receive greater attention in future research so that estimates of effectiveness can more confidently inform public policy?

Table 29.2 Summary of the reductions in caries in children in studies of different designs (cross-sectional concurrent controlled and a multilevel ecological study) and with different outcome measures [28–30]

Measure	No. of studies	Findings
Rugg-Gunn and Do [29]		**Cross-sectional controlled studies**
dmft	19	44% median reduction with fluoridation (range 29–68%)
dft	2	47% median reduction with fluoridation (34–59%)
dmfs	7	33% median reduction with fluoridation (14–66%)
dfs	1	17% reduction with fluoridation
DMFT	37	37% median reduction with fluoridation (5–85%)
DMFS	12	29% median reduction with fluoridation (0–50%)
DFS	2	27% median reduction with fluoridation (10–44%)
Do and Spencer [30]		**Multilevel ecological study**
dmfs		39% mean reduction (95% CI 18–56%)
DMFS		37% mean reduction (95% CI 15–53%)

29.4 Understanding Heterogeneity and Bias in Studies of Water Fluoridation

It is clear from the evidence that emerged across the phases of the research on water fluoridation that a consistent finding is that water fluoridation is associated with a reduction in caries in children and adolescents. However there appears to be a reasonable level of heterogeneity in the actual effect size of the reduction of caries within studies of the same design and across study designs. Bias is a process at any stage of inference tending to produce results that depart systematically from true values [31].

True differences may exist between the findings of studies of the caries preventive effect of water fluoridation, particularly when studies are conducted in very different settings. Some heterogeneity may also be due to chance or random variation. Alternatively, differences may arise due to bias or systematic error. The risk

of bias has been related to study design. However, all studies of whatever design may be biased. So, while risk of bias may start with study design, other sources of bias need to be considered.

The following sections begin with consideration of study design as a risk of bias and consider several common sources of bias: confounding, contamination, and observer bias. In later sections, sources of bias associated with measurement of exposure and outcomes will be considered in greater depth.

29.5 Study Design and Bias

Study design is considered an indicator of risk of bias. The risk of bias associated with different study designs has been ordered into a hierarchy [32]. As water fluoridation is an intervention, the hierarchy for intervention studies is relevant. A systematic review of randomized controlled trials and at least one randomized controlled trial are at the peak of the hierarchy followed by a pseudorandomized controlled trial. No studies of water fluoridation fit these descriptions. Comparative studies with concurrent controls are at the next level. Numerous study designs fit this description. Nearly all studies of the effectiveness of water fluoridation are observational comparative studies with concurrent controls. This has led some to automatically brand the evidence on water fluoridation and caries as weak [33].

While study design is widely accepted as a primary criterion for assessing the susceptibility to risk of bias, there are criticisms. Even the acceptance that randomized controlled trials are of the greatest validity (or reduced risk of bias) has been criticized. Rothman [34] contends that it is a misconception that the comparative validity [or the reduction of the risk of bias] can be inferred from the type of study. It was argued by Rychetnik et al. [35] that study design is only one aspect of the assessment of quality (or risk of bias). There is a need to understand bias in studies in order to differentiate quality, particularly within a single level of evidence. Sources of bias include:

- Confounding
- Contamination
- Observer bias

Randomization is not feasible for a population intervention like water fluoridation. Therefore, there is a need to consider biases that arise from confounding due to differences between groups either at the initiation of a study or that emerge across time. The more similar the intervention and control groups, the less the risk of bias from confounders in comparative studies with concurrent controls. However, establishing how many or exactly what confounders need to be controlled varies considerably across studies. The consideration of confounders should be driven by conceptual models of the determinants of caries, each factor should be investigated for its relationship with the "exposure" and the "outcome," and appropriate analytic approaches should be pursued to adjust estimates of effect size.

Possible confounders in any comparative study with concurrent controls include sociodemographic/socioeconomic status: age and sex; parental/household social position (income, education, employment); and issues like rurality. Dietary pattern variation consumption of sweetened drinks may also be a confounder.

The abundant availability of other preventive services may vary across the intervention and control groups and lead to a "dilution" of the effect [36]. But if "dilution" is unequally distributed across intervention and control groups, it may create confounding. A special case of an unequal distribution of other preventive measures is co-intervention. Co-intervention occurs when members of the control group receive other effective interventions as a substitute for the intervention [37], in this case exposure to fluoridated water. Such a situation might involve a school-based fluoride rinsing program or application of fluoride varnish.

There are further factors that might bias studies around water fluoridation. Contamination is where the intervention is obtained in part or full by some in the control group. This is recognized as the "diffusion" of fluoride exposure into the control group via foods/fluids produced in a fluoridated area [36, 38]. Little progress is made on how to quantitatively measure and adjust for diffusion.

Observer bias may arise when the exposure status of either individuals or a group is known when outcomes are being assessed. Exposure means that a person has, before developing caries as a disease outcome, come into contact or ingested fluoride from drinking water [31]. In most studies of water fluoridation, the exposure status of groups is known to observers of the caries outcomes, and therefore observers may be biased.

Observer bias is reduced through blinding, but this has proved impractical in most research on water fluoridation. While blinding is theoretically important, there is no strong evidence that different findings exist between blinded and non-blinded studies of water fluoridation. Just one study has attempted blinding [39]. Its results were very similar to other studies of water fluoridation.

There is a movement toward greater consideration of the consequences of a lack of blindness. Sackett [37] argues that the consequence of a lack of observer blindness should be tested through reliability testing against a blind adjudicator. Fortunately, oral epidemiology places a strong emphasis on examiner reliability, including the use of a "gold" examiner, so this is an area that studies

on water fluoridation and caries should work to strengthen. It may also be argued that as many study participants may have mixed exposure histories, knowledge of current residence in a fluoridated or non-fluoridated area may not directly create an opportunity for observer bias.

Rychetnik et al. [35] considered that there needs to be an improvement in the understanding of bias and pragmatism about the importance of study design relative to other impacts on the risk of bias and assessment of quality. New study quality assessment tools place more emphasis on the quality of what was done. Sanderson et al. [40] identified a range of domains in tools to assess the level of evidence in observational studies. These included selecting participants, addressing design-specific sources of bias (recall bias, observer bias, loss to follow-up), methods for controlling confounding, analytic/statistical methods, and conflicts of interest, all of which are relevant to the susceptibility to risk of bias. Finally, a greater emphasis needs to be placed on measuring exposure and outcomes.

29.6 Exposure to Fluoride in Drinking Water

A further source of bias in studies and a source of heterogeneity in effect size across studies on water fluoridation relate to measurement of the exposure. Exposure means that an individual or group has, before the development of caries as the outcome, drunk fluoridated drinking water. As caries is a chronic, accumulating disease, that contact takes place over time. There are several ways of characterizing exposure to fluoridated drinking water. Choice of an appropriate exposure measure is made based on an understanding of the pathophysiology of caries and the biological mechanisms of the effect of fluoride on caries as a process.

29.6.1 Exposure: Induction Period

Early research around fluoride was focused on dental mottling, a developmental change in the tooth enamel characterized by opacities in its mild forms and breakdown of the integrity, pitting or flaking, of enamel in its more severe forms. The identification of fluoride occurring naturally in water supplies as the causative factor led to the term dental fluorosis. It is, therefore, not surprising that initially the action of fluoride in the prevention of caries was thought to be due to the incorporation of fluoride into the mineralizing hydroxyapatite crystals of enamel in the form of fluorapatite which was regarded as stronger. A greater understanding of cariology led to strength being replaced by resistance to demineralization. This can be described as a preeruptive mode of action.

The successful introduction of fluoridated toothpaste clearly indicated modes of action that operate after the mineralization of the tooth. Actions on the oral microflora and on the kinetics of demineralization and remineralization at the tooth surface became more prominent. These can be described as posteruptive modes of action.

The possible modes of action are important background to different induction periods of exposure to fluoride in drinking water and caries outcomes. Exposure to fluoride in drinking water during tooth mineralization is commensurate with a developmental "critical period" exposure. Exposure to fluoride after eruption of teeth and across a subsequent lifetime is commensurate with a "lifetime accumulation" exposure [41].

A narrative review by Beltran and Burt in the 1988 [42] examined clinical and observational research and concluded that 80 percent of the benefit of exposure to fluoride was posteruptive (topical) and 20 percent was preeruptive (systemic). Yet, the importance of different possible actions remains an area of contention. Observational research in the first community water fluoridation trials [24, 43], a replication study in the Netherlands [44], and hypothesis driven research in Australia [45]and Korea [46] all support a discernable role for preeruptive exposure in permanent dentition caries outcomes among children.

This highlights the need for care in considering both the timing of exposure and the length of time the exposure to water fluoridation lasts. The key underlying question is whether the exposure occurs across a relevant induction period [47]. Induction periods are usually defined for disease initiation, but here the induction period is one for disease prevention.

29.6.2 Exposure to Naturally Occurring Fluoride in Early Research

The earliest oral epidemiology on fluoride in drinking water and caries was conducted as dose-response research across populations with exposure to differing fluoride levels occurring naturally in water supplies. Exposure can be considered at a population level or at an individual level, sometimes a combination of the two levels.

Dean and colleagues characterized the differing exposures at a population level. However, Dean et al. also applied an element of an induction period by including only children "continuously exposed to the variable under investigation (the public water supply)," i.e., who had been in the community since birth and had

drunk the local tap water [11]. Dean was analyzing dose-response for caries among children with a lifetime of exposure to drinking water at various fluoride levels.

29.6.3 Exposure to Water Fluoridation: The First Community Trials

There are a great many publications that arose out of the first four community fluoridation trials over the 16–17 years of follow-up observed. Just as in the original dose-response research of Dean et al., child participants had to have resided in the city for the whole duration of the trial. For instance, Ast et al. [24] describe "This report [on the Kingston-Newburgh trial], however, is based only on those children who had been in continuous residence in Newburgh …, or who had been born there subsequent to that date and lived continuously in Newburgh to the time of the examination."

Further, findings of the trials noted that a child born before the implementation of water fluoridation could only have a fractional life exposure depending on their age at the time fluoridation commenced and the length of time over which follow-up occurred. Arnold [43] noted that in the Grand Rapids-Muskegon trial, water fluoridation effectively reduced caries in children who were continuously exposed to its effects from birth onward. However, Arnold also pointed out beneficial effects for those born prior to fluoridation. The size of the benefit in caries prevention observed was related to the proportion of life an age group had spent exposed to a fluoridated drinking water supply. Emphasis was given the developmental stage different teeth were at the time of the fluoridation of water supplies. This would be consistent with a critical period of exposure. The presence of a smaller preventive benefit among teeth which were developed prior to the implementation of water fluoridation would support a lifetime accumulation exposure hypothesis.

29.6.4 Reviews of Community Fluoridation Trials

Reviews like that of McDonagh et al. [26] (the York Review) and the more recent review by Iheozor-Ejiofor et al. [48] (the Cochrane Review) applied an inclusion criterion to the identified before and after non-randomized controlled studies that the follow-up period needed to be 3 years. The origin of the 3-year threshold is uncertain. It does match the traditional study period for randomized clinical trials of preventive agents, being particularly prominent in toothpaste trials for caries prevention. However, such a short period is at odds with the original dose-response research and fluoridation community trials.

Given the wide age range of children studied, from preschool children aged 4 years old to early teens aged 13–16 years old, the exposure to fluoridated drinking water may have been only a small proportion of a child's life at times of outcome assessment. The exposure may also sit uncomfortably as either a critical period exposure or a short accumulation exposure, or a bit of both.

It is clear from the McDonagh et al. review [26] but not from the Iheozor-Ejiofor et al. review [27] that years of exposure was considered a factor contributing to heterogeneity of the findings. The heterogeneity of the estimates of effectiveness associated with years of exposure calls for more attention to be paid to the exposure period. The inclusion of years of fluoridation as a covariate in regression analyses for heterogeneity in systematic reviews is but a starting point.

29.6.5 Comparative Studies with Concurrent Controls: Continuous Residence or Lifetime Exposure to Fluoridated Water

A common scenario of monitoring the effectiveness of water fluoridation post-1975 has been the cross-sectional concurrent controlled study. In general, this comparison has commented less on causality and more a confirmatory documentation that differences between those exposed and not exposed to water fluoridation still exist and are in the expected direction.

Unlike the before and after non-randomized controlled study, the counterfactual assumptions cannot be directly tested: first, that there is no difference between groups before exposure to fluoridated drinking water and, second, that the difference between the exposed and not exposed groups is due only to the exposure alone. Clearly these studies are at risk of bias, and some of these have been discussed earlier. However, in cross-sectional studies with concurrent controls, the issue of the measurement of exposure and the relevance of the induction period still exists.

A frequent application of the exposure measure in cross-sectional comparisons with concurrent controls has been the exclusion of children who have not had continuous residence in either the fluoridated or non-fluoridated area. In large national studies, this exclusion occurs at the stage of analyzing data. Research in the USA has nearly always been confined to children who are continuous residents at sites, combining an ecological approach with an individual exposure criterion [49]. A substantial proportion of children may not

be continuous residents of the sites, anything up to two-thirds of participants. This applied to Brunelle and Carlos's report on the 1986–1987 National Survey of US Schoolchildren and the difference in caries for continuous residents in fluoridated and non-fluoridated sites. A further example of this was the exclusion of more than half of the children in the 1986–1987 National Survey of US Schoolchildren in Heller et al.'s [50] analyses of a dose-response to fluoride levels in water supplies. This exclusion is a way of optimizing the estimate of effect size of water fluoridation. It is no longer documenting the effect of fluoridating a drinking water supply on a population which will always have a mix of exposure levels due to residential mobility, consumption of non-tap water, or use of effective drinking water filters. It is testing an association if all children comply with or adhere to the intervention protocol and have or not have an exposure across their lifetime to water fluoridation.

Some research has extended further into measures of individual exposure. This was proposed by Grembowski [51] when researching the impact of water fluoridation on the oral health and treatment costs of young adults in Washington state, USA. Grembowski proposed a measure of percent lifetime exposure to fluoridated water. The number of years people consumed fluoridated water in their lifetime was calculated from residential histories and national censuses on fluoridated water supplies (such censuses usually give the fluoride level and the year in which fluoridation was implemented). As fluoridation exposure is determined partly by age, Grembowski calculated the percentage of a person's lifetime exposed to fluoridated water. Lifetime fluoride exposure was found to be strongly associated with caries outcomes [52].

The same concept has been extensively used in research in Australia looking at water fluoridation and childhood caries outcomes. Slade et al. [53] used residential histories and documentation of the fluoride status of all communities over 200 people to map the percent lifetime exposure to fluoridated drinking water. Lifetime exposure to fluoridated water was found to be associated with caries outcomes, stronger for the primary dentition than the permanent dentition and in a state with lower population coverage by water fluoridation. This was explained by possible action of the diffusion effect, whereby the processed foods and fluids in a fluoridated area are transported into non-fluoridated areas introducing a "contamination" in the exposure pattern. The application of such individual measures of exposure changes subtly the research question. It is no longer a question of the effectiveness of a fluoridation program at a population level, but strength of association between exposure to fluoridated drinking water and caries outcomes. One advantage of this approach is that it creates a type of dose-response relationship. Further, by mapping the period of life with exposure to water fluoridation, the relative importance of the critical period or accumulation hypothesis can be tested as was done by Singh et al. in 2003 [45].

29.6.6 Lifetime Exposure to Fluoridated Water Among Adults and Older Adults

The measurement of exposure is even more important as the age group targeted in research increases. The issue of the effectiveness of water fluoridation in adults is a crucial issue in establishing the benefits of water fluoridation in a wider population than children and adolescents and to expressions of cost-benefit. Reviews like that of Griffin et al. [54] have estimated the effectiveness of water fluoridation in adults. They found that in five studies published after 1979, the preventive fraction was 27% (95% CI 19.4, 34.3%). Griffin et al. [54] stated that most adults in the included studies had lived all their life in the fluoridated or non-fluoridated area or the studies estimated the effect of exposure to fluoridated water controlling for potential confounding variables. However, it is not certain to what extent adults were excluded from analyses of the included studies under a lifetime residency inclusion criterion.

Do et al. [55] took a different approach in a recent primary study. They mapped out the exposure pattern of Australian adults (14+ years old) using a national oral health survey dataset complied in 2004–2006. All age groups had the potential of less than all their lifetime exposed to fluoridated water. However, the exposure profile of groups depended on their year of birth and the year at which water fluoridation was introduced in whatever cities they had had residence. The mean percent lifetime exposure and the interquartile range presented in ◘ Fig. 29.3 steadily decreased across older deciles of adults. If accumulation across a lifetime of the action of fluoride is important to the beneficial effect, then older adults can at best only show a partial effect. However, older adults are also unlikely to have an exposure in their early life given they may have been born prior to the implementation of fluoridation. If there is a critical period, then older adults will not have received this benefit.

The pattern of lifetime exposure to water fluoridation has a strong effect on the association of water fluoridation and adult caries. This is apparent in ◘ Table 29.3. Estimation of the effect size of water fluoridation in adults for the highest exposure quartile in younger age groups was significant, but the effect fell away in the 45+ age groups. A truncated distribution of percent lifetime exposure to water fluoridation contributes to this null finding.

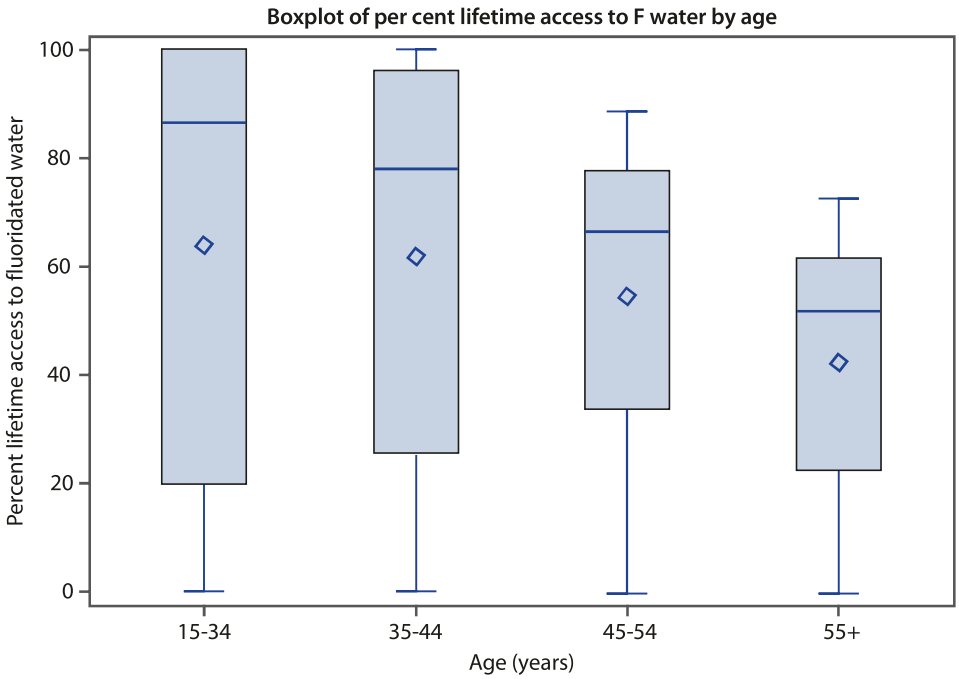

Fig. 29.3 Distribution of percentage lifetime exposure to water fluoridation by age groups in the Australian adults [55]. (Permission 19/03/19.) Rectangular box: interquartile range (IQR); small diamond: mean; horizontal line within the box, median; horizontal T lines, max and min values

Table 29.3 Adult caries outcome (DMFS) by percent lifetime exposure to water fluoridation (Do et al. 2017)

		Age		
% lifetime exposure to water fluoridation	15–34	35–44	45–54	55+
	Mean ratio			
Lowest quartile 0–20; 0- < 26; 0–34; 0–23	Ref	Ref	Ref	Ref
Highest quartile 100; 100; 78–89; 61–73	0.67 (0.48–0.92)	0.78 (0.66–0.93)	0.93 (0.82–1.04)	1.00 (0.93–1.08)

Water fluoridation is likely to be effective beyond the age of 35 years old. In addition to the issue of truncation of exposure, there is a likely saturation of the sites in the mouth which are likely to develop caries which obscures variation in the caries outcome measurement (See ► Sect. 29.7.2).

29.7 Caries Outcomes

29.7.1 Background

The caries process is continuously occurring in all individuals. However, in most individuals and at most sites in the mouth, the process ebbs and flows between demineralization and remineralization and basically is at an equilibrium. Occasionally, a local or a more generalized change in the oral environment will tip the process out of equilibrium, and demineralization will become dominant. If that continues for long enough, irreversible damage will occur to the enamel, and the underlying dentine of a tooth and a carious lesion will have formed. Such a lesion may go undiagnosed and extend. Alternatively, it may be diagnosed, and an intervention in the form of a filling could be placed. If the process is left undiagnosed or is not successfully treated for a long period of time, then deeper tissues within the tooth or at the apex of the root of the tooth may become involved, and a tooth may need complex treatment, or the tooth may be extracted.

Capturing observations of caries outcomes is a fundamental part of all oral epidemiology of caries. The methodology of oral epidemiological fieldwork is dominated by procedures for examiners to follow and criteria to be applied in making judgments about the presence

or absence of caries, now or in the past, at a tooth or tooth surface-level.

Most epidemiology focuses on the prevalence or incidence of a disease. Both are available as outcome measures for caries. However, more frequently oral epidemiological research is measuring prevalence and severity. In measuring severity oral epidemiology seeks to differentiate between individuals by the extent of caries experienced. This is done by calculating summary scores, the summed number of decayed, missing due to decay (extracted) or filled (due to decay) teeth (DMFT) or tooth surfaces (DMFS). When these measures refer to children's primary dentitions the nomenclature to use is lower case dmft/s, and when referring to the permanent dentition, the nomenclature to use is upper case (DMFT/S). Oral epidemiologists are so used to these measures that there is a risk that the different character of them and the relationship between them is not considered or explained. This can be a source of measurement bias. Understanding this risk depends on the underlying natural history and intraoral distribution of caries.

29.7.2 Natural History and Intraoral Distribution of Caries

The observable signs of caries and the summary measures for caries follow working rules. These are underpinned by a hierarchy of "zones" of caries attack first described by an Expert Working Group of the World Health Organization (WHO) as part of the International Dental Epidemiological Methods Series in 1967 [56]. Poulsen and Horowitz [57] examined this hierarchy against three separate studies data and offered some modifications, but the basic hierarchy was confirmed (Table 29.4).

Table 29.4 Hierarchy of teeth and tooth surfaces involved in the caries attack [56]

Zone	Description of teeth and surfaces involved
5	Proximal surfaces of mandibular anterior teeth (excluding distal surfaces of cuspids)
4	Labial surfaces of maxillary and mandibular incisors and cuspids
3	Proximal surfaces of maxillary anterior teeth (excluding distal surfaces of cuspids)
2	Proximal surfaces of posterior teeth (including distal surfaces of cuspids)
1	Pit and fissure surfaces of posterior teeth
0	None of the above

Bachelor and Sheiham [58] confirmed that the most susceptible tooth surfaces to decay are occlusal surfaces of first molars and buccal pits of lower first molars. If all the first molars have caries, then there is a high probability that the second molars will be affected. The occlusal surfaces of the second molars and the buccal surfaces of the second lower molars are the second most susceptible sites for caries. At higher DMFS, the mesial proximal surfaces on the upper molars are the next sites to be affected and then the lower proximal surfaces. These are followed by the occlusal surfaces of the first premolars and proximal surfaces of first molars and then the occlusal surfaces of second premolars and the proximal surfaces of second molars. These are followed by the occlusal surfaces of the second premolars and then the upper first premolars. At higher levels of caries, all surfaces of canines, smooth surfaces of premolars, and incisors are affected. Sheiham and Sabbah [59] extended the discussion of working rules on the natural history of caries. These working rules have relevance to understanding the heterogeneity in estimates of effect size and bias in the measurement of caries outcomes.

First, there is a defined relationship between caries prevalence and DMFT. This relationship was reported on by Knutson in 1958 [60] using data from the first series of fluoridation trials in the USA. Knutson defined the relationship with a catalytic equation $K\text{-}PREV = K^*(B)^{DMFT}$ where DMFT is the age-specific caries severity, PREV is the age-specific caries prevalence, and B and K are constraints for all age groups and populations. Others have tested the relationship with newer data and confirmed the working rule [61, 62]. The catalytic nature of the relationship captures a very rapid rise in prevalence against a slowly rising DMFT across modest DMFT scores, but then a plateauing of prevalence across higher DMFT scores. As the general relationship holds across age groups and populations, it assists in understanding the different estimates of effect size between prevalence and caries experience expressed as either dmft or DMFT (see Table 29.1 for the variation).

Second, there is a defined relationship between DMFT and DMFS. Again, this was first defined by Knutson [60]. However, understanding this relationship relies more on the hierarchy in the observed pattern of caries attack of teeth and tooth surfaces. As higher zone teeth and tooth surfaces become involved in the caries process, measures of caries experience will increase. This has been the basis of using observations on the involvement of zones to predict actual caries experience scores. However, a different aspect of this hierarchy of caries attack underlies the behavior of caries experience

outcome measures. Progression to higher zones also involves a general movement from posterior to anterior teeth and pit and fissure to proximal to free smooth surfaces being involved in the caries attack. Thus, pit and fissure surfaces of posterior teeth are the first teeth and surfaces and the proximal surfaces of the same posterior teeth are the next surfaces to show evidence of the caries attack. Progressing from Zone 1 to 2 may not involve a change in DMFT score, but DMFS will be higher for those who have reached Zone 2 in the caries attack process. A similar disconnect occurs for free smooth surfaces and proximal surfaces of various anterior teeth. Both DMFT and DMFS will be higher as one progresses to higher zones, but the rate of increase will not be linear or equal.

Water fluoridation is known to prevent caries in a preferential manner from free smooth surfaces to proximal surfaces to pit and fissure surfaces [63]. A consequence of this is that free smooth surfaces of anterior teeth are more likely to be saved from caries ahead of proximal surfaces of anterior teeth, and proximal surfaces of posterior teeth are likely to be saved from caries ahead of pits and fissures of those same teeth. A working rule of caries is that as caries in populations is successfully prevented, caries in the least susceptible surfaces (free smooth and proximal surfaces) decreases considerably more than in the most susceptible surfaces (pits and fissures) [64].

The pattern of teeth and tooth surfaces affected by caries and the preferential benefit of water fluoridation across different surfaces explain two issues in the evidence on effect size for caries prevention by water fluoridation. These are:

- The variation across measures for prevalence and caries experience and within caries prevalence at the tooth and surface level
- The finding that higher baseline caries experience is associated with larger effect size

The size of the percentage reduction in caries outcomes appears greater in situations where there is more caries activity and when caries outcomes are measured at the tooth surface level than tooth level than at the level of prevalence. Similar consideration underlies the differences observed in the effect of water fluoridation in the primary and permanent dentitions.

Brunelle and Carlos [65] reported on the 1986–1987 US National Survey of Schoolchildren. They reported a greater percentage reduction in caries at the surface level in the primary dentition of 5-year-olds (39%) than in the 12-year-olds (17%) [49].

29.8 Alternative Caries Outcome Measures

A feature of caries experience measures is that each of the possible presentations, an untreated carious tooth, a missing tooth, and a filled tooth, contributes equally to the summed tooth-level score. Yet, these presentations may represent quite different extent of disease on an individual tooth. A similar situation exists for the summed score at the tooth surface level, although there are attempts to adjust for the number of surfaces a missing tooth might contribute to the summed score.

There have been proposals to weight the components in a way that reflects the number of functioning teeth or sound tooth substance present. Sheiham et al. [66] proposed the functioning teeth and T-Health indices. The functioning teeth index is an aggregate of the number of filled (otherwise sound) teeth and sound teeth, each being of equal value. This presupposes that sound and restored teeth have, all other things equal, equivalent function and benefits. The T-Health index represents the amount of sound tooth tissue. A sound tooth will contain more sound tooth tissue than a filled tooth, while the latter was proposed to have more sound tissue than a decayed tooth. Later, filled and decayed teeth were considered to have the same amount of sound tooth substance [67]. Missing teeth have no sound tissue.

Jakobsen and Hunt [68] used data from three national oral health surveys in the USA and a state level survey in Iowa to show that functioning teeth and T-Health indices were more capable of detecting changes in oral health than the traditional DMF index. Birch [69] used a similar approach to the T-Health measure to simulate the effect of water fluoridation on oral health. Birch assigned values to the presentation of each tooth – sound, filled, filled and decayed, and decayed and missing – and used the sum as a "quality-adjusted tooth stock." Others like Fyffe and Kay [70] have explored more complex utility functions. Lewis [71] examined weighted indices and utility functions from the DMF index. Lewis concluded that a utility-weighted version of the DMF index has more theoretical validity, but that it does not necessarily lead to more sensitive outcome measure of caries.

The dominance of the traditional caries prevalence and experience measurement in the oral epidemiology around water fluoridation is somewhat unfortunate. Such measures are not readily interpretable by the public. Some effort has gone into other self-reported measures that have more ready interpretation. Self-reported measures of oral health such as a global rating of oral health or a version of oral health-related quality of life might be more reflective of community valuations of oral health outcomes [72].

29.8.1 A Different Approach: Incidence and Increment of Caries

Some of the concerns with the risk of bias with exposure measurement and measurement of outcome might be reduced if rather different study designs were more commonly pursued in research about the effectiveness of water fluoridation. Cohort studies which follow exposure and the incidence or increment of caries across time offer advantages in studies among adults. Exposure can be determined across a relevant time, possibly as short as that adopted for clinical trials. Outcome can be measured by tracking the change in tooth surface status. This may circumnavigate the problems of exposure for only a fraction of a full lifetime and the recurrence of caries at teeth or tooth surfaces that have already experienced caries and therefore show no increment in the summed scores for caries experience. This is especially relevant in middle and older-aged adults where the caries experience may approach saturation.

One such study was conducted by Hunt et al. [73] in Iowa among an older adult population, 65 years old or more. The incidence of caries was compared among those long-term residents in a fluoridated and non-fluoridated community. Exposure was therefore a combination of an ecological measure with an element of individual exposure history as an inclusion criterion. Exposure was measured over a 30-year period, implying a need for a long lead time for accumulation of fluoride's action. The incidence of caries across an 18-month period was lower in those adults who had resided in a fluoridated community for more than 30 years. Hunt et al. concluded that water fluoridation appeared beneficial even though exposure to fluoridated water began in adulthood and therefore fitted a posteruptive exposure and accumulation hypothesis.

This study provides an indication of evidence that can be obtained in a relatively short time period. Refinement of the way exposure is measured at an individual level might see such an approach have greater applicability especially among adults.

29.9 Conclusions

A benefit of water fluoridation in the prevention of caries is a consistent finding in all the stages of development and implementation of water fluoridation as a public health measure. These include dose-response studies, community fluoridation trials, and monitoring of the outcomes of fluoridation programs. However, there is a good deal of heterogeneity in the effect size across individual studies. This heterogeneity reflects different study designs and the risk of bias. Confounding, contamination, and observer bias are frequently considered as sources of bias. Two additional sources of potential bias are examined: measurement of exposure and outcome. There are many ways in which measurement of exposure and outcome can contribute to study findings not reflecting a true result, that is, being biased. Hopefully consideration of these measurement issues will lead to greater attention being paid to them in the interpretation of the results of existing studies or in future studies of water fluoridation.

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