BMJ Open

Toothbrushing programme in Saudi Arabia 'TOPS': a study protocol for a cluster randomised controlled trial in kindergartens, Riyadh

Budur Almutairi ,[1,2] D Conway,[1] Alastair Ross,[1] Mohammed Hattan,[2] Fayyad Almogren,[2] Alex D McMahon[1]

To cite: Almutairi B, Conway D, Ross A, *et al*. Toothbrushing programme in Saudi Arabia 'TOPS': a study protocol for a cluster randomised controlled trial in kindergartens, Riyadh. *BMJ Open* 2024;**14**:e083504. doi:10.1136/bmjopen-2023-083504

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2023-083504).

Received 20 December 2023
Accepted 16 July 2024

[1]School of Medicine, Dentistry, and Nursing, University of Glasgow, Glasgow, UK
[2]Saudi Arabia Ministry of Health, Riyadh, Saudi Arabia

Correspondence to
Budur Almutairi;
2170410a@student.gla.ac.uk

ABSTRACT

Introduction Dental caries among children is a major global health problem and is a particular public health challenge in Saudi Arabia. Dental caries cause pain, infection and negatively impact quality of life. As part of population oral health improvement efforts in Saudi Arabia, this project aims to evaluate the effectiveness of a supervised toothbrushing programme in kindergartens.

Methods and analysis This study is a cluster randomised controlled trial. Enrolment began in September 2022, for two academic years (2022–2024) on 20 randomly selected kindergartens in Riyadh. The data collection phase will be completed in September 2024. Ten kindergartens are randomly allocated to supervised toothbrushing and 10 to treatment as usual, which is an annual oral health awareness visit. The primary endpoint will be the worsening of obvious decay experience as measured by decayed (into dentine), missing and filled teeth (d3mft) from baseline to the second year of follow-up. The secondary endpoint will be the increase in the number of teeth affected. A priori subgroups of the region of Riyadh, school type (public, private), child sex and presence/absence of prior decay at baseline, will be analysed. We require 244 evaluable endpoints using a power of 80% to meet the sample size requirement. In addition, questionnaires on behaviours, quality of life, process monitoring and cost analysis are being deployed.

Ethics and dissemination Ethics approval for this study was given by the King Fahad Medical City Institutional Review Board in the Saudi Ministry of Health (22-083E/March 2022). The data analysis has been approved by the University of Glasgow Medical Veterinary and Life Sciences Research Ethical Committee (200220194/March 2023). The results of this study will be disseminated through presentations at scientific conferences and in scientific journals.

Trial registration number NCT05512156.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study design, which investigates the efficacy of supervised toothbrushing in the two academic years of kindergarten, reflects exactly the population for which the intervention could be rolled out if the study has a positive conclusion.
⇒ A methodological strength of this study is that because the primary endpoint is 'worsening of decay,' this means that children with pre-existing decay are eligible for inclusion in the study. This is essential for the generalisability of the final results and allows us to use prior decay as a subgroup for analysis.
⇒ The study was powered to detect a treatment difference of 15% versus 30% in the primary endpoint, resulting in a sample size of 122+122 = 244 children, which was inflated to a randomised number of 153+153 = 306 to allow for a dropout percentage of 20%, in 10+10 = 20 schools.
⇒ We are also collecting quality of life data from the Child Health Utility 9 Dimensions questionnaire, additional cost data for the intervention arm, and behavioural and dental health services data and will also conduct an integrated process evaluation of the trial.
⇒ The availability of Kindergarten Level Two children, who are the participants of this study, in public schools is limited compared with private kindergartens.

INTRODUCTION

Dental caries of the primary dentition is the most common prevalent childhood condition as identified in the Global Burden of Disease study with 514 million children being affected worldwide.[1] The WHO Global Oral Health Status Report stated that the disease burden has been reported to be particularly high in the Eastern Mediterranean Region.[2] A recent nationwide oral health survey of school children across Saudi Arabia reported an overall prevalence of 66% for dental caries, with 72% occurring in primary teeth and 62% in permanent teeth in 2023.[3]

Oral health improvement programmes in educational settings such as kindergartens and schools are particularly important because oral health initiatives can be implemented and reach children at a young age and on a population scale.[4] A recent systematic review revealed that the implementation of daily

supervised toothbrushing in educational settings can lead to a significant reduction of 30% in decayed, missing and filled teeth (dmft) when compared with the control group that solely received oral hygiene instructions.[5] However, there have been a few randomised controlled trials of supervised toothbrushing programmes, particularly in areas with high caries or where other oral health improvement programmes or initiatives are in place such as water fluoridation. Three trials (all conducted in Europe or North America) found that caries reduction in children receiving supervised toothbrushing compared with control ranged from 24% to 56%.[6–8]

However, there have been no studies conducted in Saudi Arabia to date, nor there have been any studies evaluating supervised toothbrushing programmes where the public water supply is fluoridated. The potential of implementing and evaluating daily supervised toothbrushing in early years educational settings in Riyadh, Saudi Arabia where there is community water fluoridation could contribute to preventing dental caries in the childhood population.[9]

STUDY OBJECTIVE

The objective of this study is to compare the effectiveness of supervised toothbrushing with treatment as usual (TAU) in preventing any further dental decay from developing.

METHODS AND ANALYSIS

Study design

Basic design: cluster randomised toothbrushing in kindergartens in Riyadh KSA.

Group 1—Supervised Toothbrushing plus TAU.

Group 2—TAU.

The design is described diagrammatically in figure 1 (flow diagram of the TOPS study).

Study enrolment began in September 2022, and data collection will be completed in September 2024.

Study population

One hundred and fifty-three children will be recruited into each of the two arms of the study. They will be identified in 20 kindergartens from public and private schools in Riyadh city including the North and East regions. The average age of children at recruitment will be 4 years old attending the second (year) level of kindergarten schools (KG2). The children's approval to participate will be assessed by consent forms that will be sent (along with participant information sheets) to parents through the kindergartens before the commencement of the study.

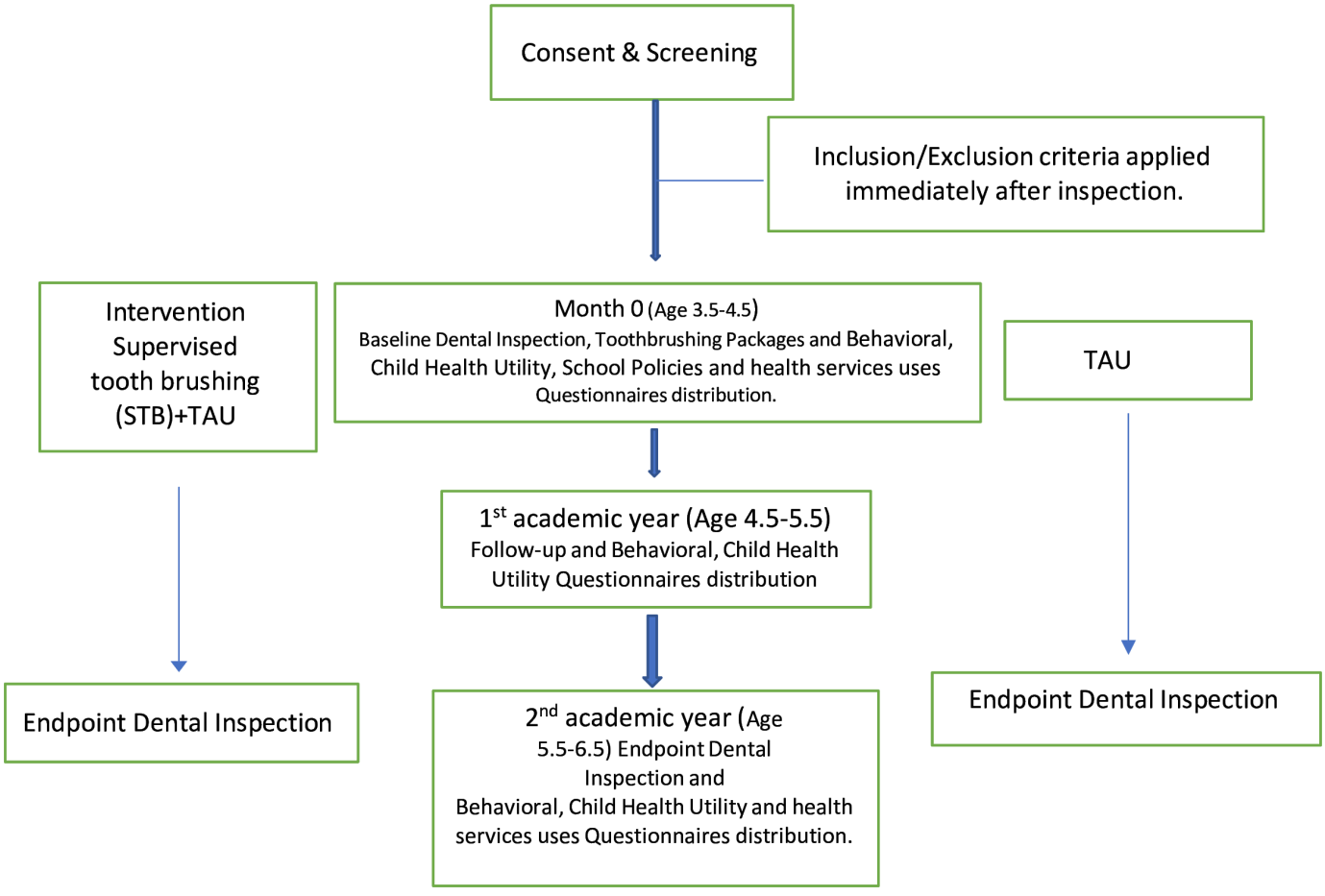

Figure 1 Flow diagram of the TOPS study. STB, supervised toothbrushing; TAU, treatment as usual.

Inclusion criteria

- Receipt of a signed informed consent form from a parent or legal guardian.
- Children in the second year of kindergarten school (known as KG2).
- Children with or without pre-existing dental caries.

Exclusion criteria

Child is unwell on the same day of dental inspection.

Identification of participants and consent

Once the headteacher has agreed for their kindergarten to participate in the study, a consent form will be sent to the parents or guardians of every KG2 child through the kindergartens, with instructions to children to bring them home and back to school (online supplemental file 1'). On the day of the dental inspections (baseline), any child showing distress or verbal, or non-verbal signs of extreme reluctance will be excluded from the study if the dentists feel that continuing with the inspection would cause the child further distress.

Withdrawal of subjects

Parents who withdraw their child will be asked, if appropriate, to agree to have the end-of-study dental inspection examination, to make the best use of the information collected on that child. Children who leave a trial kindergarten during the study, but remain in the local area, and go on to attend a local school will receive an endpoint dental inspection (unless they have actively withdrawn from the study). The parents/guardians of these children will be informed in advance of the inspection visit to their child's school. In the event of a child having to leave the study due to withdrawn consent, or moving home and so on, the head teacher at the school will inform the study team. If the parent agrees, arrangements will be made to complete the end-of-study dental inspection to maintain that child in the study database by completing the End-of-Study Form.

Study schedule

Up to three main kindergarten visits are involved for children who are retained throughout the study. The first will be to complete the baseline dental inspection and baseline questionnaires which include a Child Health Utility 9 Dimensions (CHU9D),[10] behavioural and health and dental care services resource use questionaries distribution and to distribute toothbrush/toothpaste packs (two packs for every child every 3 months, one for use in the school and the other in the home). The second visit is after 1 year of intervention for follow-up with further distribution of toothbrushing packs and questionnaires which include a CHU9D and behavioural questionnaires. The final visit is to undertake an endpoint dental inspection to reinspect the child and to distribute the final questionnaires at the end of the study which include a CHU9D, behavioural and health and dental care services resource use questionaries. Neither children nor parents are required to make special visits to a clinic or other study base.

Visit 1: examination/0 month intervention visit.

At this visit, the study staff will confirm eligibility before the baseline dental examination is undertaken by a study dental practitioner (ie, that a signed consent form has been received, and the child has no obvious temporary oral infections or injuries that would lead to exclusion on the day). Dental inspection and collection of examination data will be completed. Packs of toothbrushes/toothpaste and questionnaires will be distributed, and the supervised toothbrushing process will be explained to both teachers and children—following established protocols and guidelines.[11]

Visit 2: one academic year (±3 months): questionnaires and toothbrushing packs distribution.

Visit 3: two academic years (±3 months): endpoint questionnaires' distribution and end-of-study dental examination visit.

This visit will be conducted when participating children are in KG3, and approximately 5–6 years old. The final dental inspection will be undertaken, and data collected accordingly, regardless of whether the sequence of the supervised toothbrushing had been interrupted or discontinued for any reason.

Study outcomes and endpoints

The main outcome measurement will be the number of teeth with obvious decay experienced into dentine for a participating child. This will be measured at both the baseline visit and after two academic years of follow-up. The difference from two academic years minus the baseline measure will then be calculated. Any negative differences will be set to zero. Negative differences can happen either due to tooth trauma or due to variations in the inspection data. This is to be expected due to the nature of tooth charting, and this is especially possible when different dentists/therapists inspect the same child.

The primary *endpoint* will be 'worsening of decay', namely an increase in the number of dmft of one or more. This variable can be coded as a binary variable with categories of yes and no. The secondary endpoint will be the increase in the number of teeth affected.

Quality of life

In addition to clinical data, information on how a child's general and oral health affects their quality of life will be collected using a CHU9D questionnaire which will be distributed at three points in the trial: at baseline, one academic year and two academic years. Also, the parents/guardians of the participants will be asked to complete a behavioural questionnaire on the health of the child's teeth, how they take care of them and the child's diet and a questionnaire on health and dental care services resource use that is designed to elicit information on the uptake of health and dental care services and medication use by the child within the past 12 months will also be distributed at each of the baseline and two academic years

rounds. The questionnaire packs will be distributed to the parents/legal guardians via the kindergarten. Several well-established techniques to enhance questionnaire response rates will be used.

These are as follows:

- The cover page for the questionnaire pack sent at baseline.
- Parents who had previously provided a mobile telephone number will receive a text reminder if they have not returned the questionnaires within 1 week.
- At the end of the second week, a second copy of the questionnaire pack will be distributed via the child's kindergarten to any non-responders.
- At the end of the third week, the non-responding parents will be contacted by telephone to remind them to complete the questionnaires.

In addition, information on school health policies about School Health Services, school physical environment, health education, school policies and resources will be collected through headteacher surveys (online supplemental file 2).

Adverse reaction reporting

If there are any immediate adverse reactions to the fluoridated toothpaste (eg, mucositis, allergy, etc), the product will be removed by rinsing. The possible adverse reaction may be noticed immediately by the dental team or later by the teachers or parents and this will be documented in the form.

Intervention

Recruitment, consent and questionnaires (Behaviours, Quality of Life, Cost Analysis) distribution.

- Mandatory training and calibration for the dental inspection team.
- Consent through kindergartens.
- Inclusion and exclusion criteria applied.
- Child baseline dental examination.
- Toothbrushes and toothpastes packs delivery (six packs per child per year—child soft toothbrush with a 1450 ppm fluoridated toothpaste).
- Kindergarten teachers training in supervised toothbrushing protocols.[11]
- Three month interval monitoring visits for toothbrush/toothpaste packs distribution, and a monitoring sheet for the number of children brushed will be used by the monitor and the supervised teacher.
- One academic year follow-up and questionnaires (Behaviours) distribution.
- Endpoint dental examination and questionnaires (Behaviours, Quality of Life, Cost Analysis) distribution.

Treatment as usual (TAU)

All children in this arm of the study will be receiving TAU which is an oral health awareness education session in the school (once per year)—covering topics including the importance of daily toothbrushing, a healthy diet and demonstrating how to brush correctly and efficiently. All children in Riyadh are exposed to background 0.6–1.5 ppm water fluoridation.[12]

Storage of study products

Toothbrushes/pastes for the intervention group will be stored in the school at the recommended storage temperature of 25°C, opened tubes will be discarded after '12 months'.

STATISTICS AND DATA ANALYSIS

The primary endpoint which is 'worsening of decay' will be tabulated and analysed by ORs, with the attendant 95% CIs and p-values. This will also be carried out for the subgroups of the region of Riyadh, school type (public, private), child sex and presence/absence of prior decay at baseline. Additionally, interaction tests will look at any possible synergy or antagonism of the treatment effect with the four subgroups (separately). Logistic regression models will be used for these analyses. The numeric value of the number of excess teeth with obvious decay (ie, the secondary endpoint) will also be analysed. All statistical tests will be carried out at the traditional 5% significance level, using the software package SAS V.9.4. There are no issues with multiple testing as the primary endpoint and analysis are clearly defined, with the other analyses being of an exploratory nature.

Sample size

The sample size calculation is based on the primary endpoint which is 'worsening of decay'. This calculation used a power of 80% and an alpha level of 5%. As this is a cluster randomised trial, the usual sample size is slightly inflated by the design effect (DE) of DE=1 + (N−1) *ICC. N is the average class size, which is assumed to be 15 children being successfully inspected and partly based on pilot data and partly based on the traditionally weak intraclass correlations (ICC) in public health that have been assumed to be 0.001, which produces a DE of 1.019. To detect a difference of 15% worsening in the toothbrushing group versus 30% in the TAU group,122 children in each group with evaluable endpoints will be required, providing a total sample size of 244 children. Note that to contribute an evaluable endpoint, a child will need valid dental inspections at both the baseline and the end of the study. However, in practice, not all of the children will complete the study. If a loss to follow-up rate of 20% is assumed, inflation of the number of children that are required to be randomised is 153 in each group, and 306 children in total. This corresponds to approximately 20 schools.

In summary:

- Randomise 153+153 = 306, from 10+10 schools.
- The sample size requires 122+122 = 244 evaluable endpoints.

Randomisation

A stratified random sampling technique was performed where schools were the unit of randomisation. A random

sampling of the school list obtained from the Ministry of Education was used to allocate schools to either an intervention or a TAU group within each stratum from both two regions (North and East) using blocks of two.

For the type of school, we have only six available public schools, so we will include all of them (three in each) and the remaining 14 of the private schools (seven in each).

Blinding

Children participating in this study cannot be blinded given the nature of the intervention. Both children and their parents will be provided with an information sheet that explains the intervention; therefore, they will know whether they will be in either the intervention or TAU group. Examiners will be blinded as children in both groups will be dealt with identically in the dental inspection visits. All outcome assessment data will be delivered to the principal investigators, and thus, each school will be identified to the allocated group according to the child's code that was generated for each child to anonymise names during data collection and analysis.

Subgroups

Some subgroups of interest will be available for study in the analyses.

1. Sex.
2. Type of school. The study will recruit from both public and private kindergartens.
3. Region of school. The study will recruit kindergartens from the north and east regions of Riyadh.
4. Dental caries at baseline. Most of the children will have existing dental caries at baseline, this will be a yes/no variable. If the decay proportion reaches over 90%, this subgroup may be unreliable.

ECONOMIC EVALUATION

Economic evaluation data sources

Trial-related resource use will be estimated using the information from direct inquiries from a staff costs questionnaire. For each trial-related visit to a participating kindergarten, the trial staff will fill in a staff costs questionnaire, which contains questions on time spent in a kindergarten delivering interventions, distance travelled (calculated from postcodes of the origin and destination of journeys), the number and type of vehicles involved in a visit to the kindergarten and the number of toothbrushing backs that were distributed. The CHU9D will allow the calculation of quality-adjusted life-years (QALYs), while the other outcome questionnaires will provide data on oral/general health-related life quality-of-life scores only.

Economic evaluation methods

The incremental costs and benefits of the toothbrushing intervention over and above TAU will be explored. The relationship between the general health and oral health-related quality of life measures and the decayed (into dentine), missing and filled teeth (d3mft) outcomes will be assessed using linear regression methods. A cost-utility analysis will also be performed: with the outcome measure being. QALYs will be calculated using responses to the CHU9D questionnaires. Both costs and health outcomes will be discounted at the same annual rate of 1.5% as per the public health reference case. Sensitivity analysis will be performed by varying such parameters as the costs of staff and the time the trial staff spent to deliver the interventions to each child. The results of the economic evaluation will be reported using a cost-effectiveness plane and Cost-Effectiveness Acceptability Curve, incorporating the currently accepted values of willingness-to-pay thresholds for a QALY as per the National Institute for Health and Care Excellence (NICE) guidelines.[13]

Intervention cost

Staff travel information and costs that are related to staff delivering the interventions will be collected. Members of staff will be asked to fill in a 'staff travel cost' form each time they visit a kindergarten. A full economic evaluation of the study will be carried out and will be reported separately following the UK's NICE public health economic evaluation guidelines.[13] Health outcomes will be expressed over the two academic years follow-up period using the CHU9D questionnaire to obtain utility scores.

DATA HANDLING

There are three distinct phases to study data management.

Phase 1. Identification and consent of study participants.

Phase 2. Dental examinations (baseline and follow-up).

Phase 3. Intervention (toothbrushing/TAU) activity recording.

Examination sheet/data record

Examination forms will be used to collect study data. Access to data will be restricted, and they will be entered by study personnel, with only authorised site-specific personnel able to make entries or amendments to their participants' data. All data handling procedures will be detailed in a Study Specific Data Management Plan. Data will be validated at the point of entry and at regular intervals during the study. Data discrepancies will be flagged to the study site and any data changes will be recorded to maintain a complete audit trail (reason for the change, date change made and who made the change).

STUDY MONITORING

Study Monitoring Visits will be conducted by the Saudi Ministry of Health (MOH) dental staff team every 3 months with toothbrushing packet distribution. A monitoring sheet will be used by the monitor and the supervised teacher. A single named person at each treatment site, responsible for overseeing the intervention, will be asked on each quarterly visit whether children have the opportunity to brush their teeth every day, and if not to explain when/why this may not be possible. They will then

be asked to give the main challenges to daily brushing (barriers) and to say what helps.

As well as quarterly monitoring visits, a dedicated survey of school health policies and practices will be carried out. This survey will be administered to Head Teachers (or other suitable education leads) at both intervention and TAU schools. This covers any ongoing contextual activity that could affect the children's oral health such as hygiene provision, nutritional services and policies, health education and resources, etc.

PROCESS EVALUATION

We will conduct an integrated process evaluation of the trial, which will allow us to:

- Describe the implementation of the intervention and data collection in schools, including barriers and facilitators to efficiency and effectiveness.
- Collate the experiences of those involved, including staff and parents.
- Make recommendations for the full roll-out of the programme in Saudi Arabia, should the trial be successful.
- Make recommendations for the carrying out of trials in early years settings, and for complex community-based trials in general.[14]

The process evaluation is guided by a simple logic model for the trial (see figure 2 logic model to guide process evaluation) which sets out intended resource use, key activities and intended short and longer term outcomes.

Patient and public involvement

Participants (children), parents, school staff and teachers were involved in the research before, during and after the start of the study. Before the start of the study, the importance of supervised toothbrushing was discussed with policymakers in the Saudi Ministry of Health and the Ministry of Education and they were involved in the recruitment and conduct of the study. Also, the preferable way and time of brushing were negotiated with children, parents and teachers. During the study, monitoring visits will keep them involved in the progress of the intervention and any challenges that occur. After the study, they will be involved in plans to disseminate the study results to participants and relevant wider public communities.

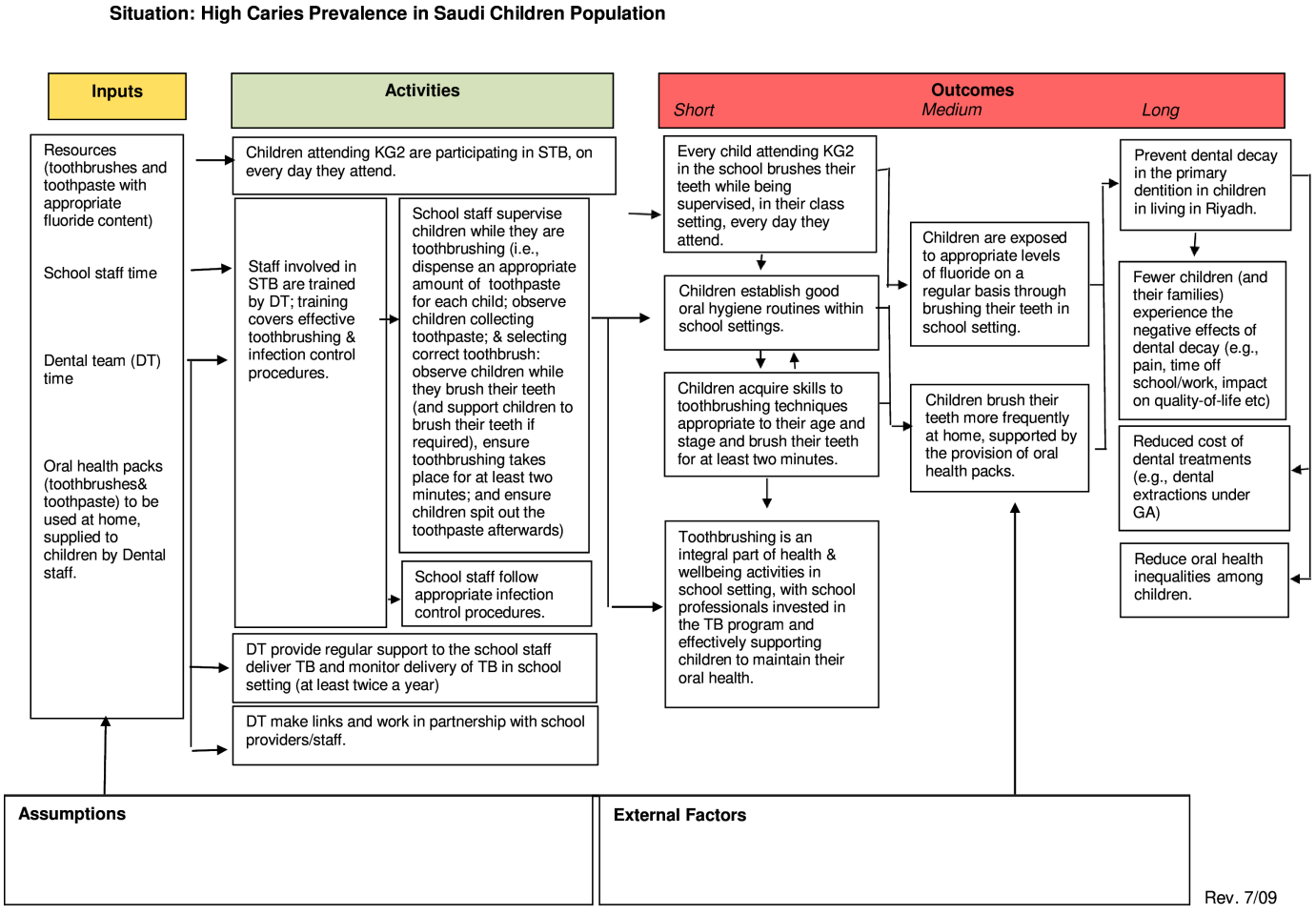

Figure 2 Logic model to guide process evaluation. Toothbrushing Programme in Saudi Arabia 'TOPS'—a cluster randomised controlled trial in kindergartens, Riyadh Logic Model. DT, dental team; KG2, Kindergarten Level Two; STB, supervised toothbrushing; TB, toothbrushing.

ETHICS

This study was approved ethically by the King Fahad Medical City institutional review board in the Saudi Ministry of Health (22-083E/March 2022). Study participants will only be allowed to enter the study once either a parent or legal guardian has provided written informed consent. The Chief Investigator will be responsible for updating the Ethics Committee on any latest information that is related to the study. The data analysis for this study had been approved ethically by the University of Glasgow Medicine, Veterinary and Life Sciences Research Ethical Committee (200220194/March 2023).

Trial registration was obtained via clinicaltrials.gov.[15]

DISSEMINATION OF FINDINGS

Study team members will collaborate on producing papers to be submitted to peer-reviewed journals and abstracts of proposed presentations at national and international conferences and symposia.

Acknowledgements The authors would like to thank the Saudi dental inspection team: Wejdan AL Harthy, Tasneem Rashid, Sarah Alshahrani, Mashael Almoghairi, Nohaiah Alnoaim, Eman Aboali, Norah Alnomsy and Reem Abo-Omar.

Contributors BA was responsible for intervention design, protocol development, supervising the dental team, data collection, data clearance, intervention monitoring, investigation, project management and evaluation. DC helped in intervention design, protocol development and academic supervision. AR contributed to the monitoring and evaluation process. ADM developed the methodology, took part in the design of the study and will conduct statistical analysis. MH supervised the study in Saudi Arabia and was involved in dental team organisation and administration. FA assisted in dental team supervision. BA is the guarantor.

Funding This work was supported by the Saudi Ministry of Health studentship (43/C/27,2022).

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Patient and public involvement section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Budur Almutairi http://orcid.org/0009-0001-6205-9839

REFERENCES

1 Who.int. Oral health. 2024. Available: https://www.who.int/news-room/fact-sheets/detail/oral-health
2 World Health Organisation. Global Oral Health Status Report: Towards Universal Health Coverage for Oral Health by 2030. www.who.int, 2022. Available: https://www.who.int/publications/i/item/9789240061484
3 Orfali SM, Alrumikhan AS, Assal NA, *et al*. Prevalence and severity of dental caries in school children in Saudi Arabia: a nationwide cross-sectional study. *Saudi Dent J* 2023;35:969–74.
4 Clark E, Foster Page LA, Larkins K, *et al*. Caries-preventive efficacy of a supervised school toothbrushing programme in Northland, New Zealandnorthland, New Zealand. *Comm Dent Health* 2019;36:9–16.
5 Bramantoro T, Santoso CMA, Hariyani N, *et al*. Effectiveness of the school-based oral health promotion programmes from preschool to high school: a systematic review. *PLoS ONE* 2021;16:e0256007.
6 Amend S, Hartmann T, Heinzel-Gutenbrunner M, *et al*. Caries experience and increment in children attending kindergartens with an early childhood caries preventive program compared to basic prophylaxis measures-a retrospective cohort study. *J Clin Med* 2022;11:2864.
7 Andruskeviciene V, Milciuviene S, Bendoraitiene E, *et al*. Oral health status and effectiveness of caries prevention programme in Kindergartens in Kaunas city (Lithuania). *Oral Health Prev Dent* 2008;6:343–8. Available: https://pubmed.ncbi.nlm.nih.gov/19178101/
8 Curnow MMT, Pine CM, Burnside G, *et al*. A randomised controlled trial of the efficacy of supervised toothbrushing in high-caries-risk children. *Caries Res* 2002;36:294–300.
9 Alshammari FR, Alsayed AA, Albakry M, *et al*. Evidence based recommendations to improve the children oral health in Saudi Arabia. *Saudi Dent J* 2022;34:431–44.
10 University of Sheffield Licensing. CHU9D - Measuring Health and Calculating QALYs for Children and Adolescents. licensing.sheffield.ac.uk, 2023. Available: https://licensing.sheffield.ac.uk/product/CHU-9D
11 Policies and Guidance – Childsmile, 2023. Available: https://www.childsmile.nhs.scot/professionals/resources/evidence/
12 Ministry of Health Saudi Arabia. Ministry of health saudi arabia. 2007. Available: https://www.moh.gov.sa/en/Ministry/MediaCenter/News/Pages/NEWS-2007-11-26-001.aspx
13 National Institute for Health and Care Excellence. NICE Guidelines. NICE, 2023. Available: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-guidelines
14 Moore GF, Audrey S, Barker M, *et al*. Process evaluation of complex interventions: medical research council guidance. *BMJ* 2015;350:h1258.
15 clinicaltrials.gov. Toothbrushing Program in Saudi Arabia "TOPS" - Full Text View - ClinicalTrials.gov, 2024. Available: https://classic.clinicaltrials.gov/ct2/show/NCT05512156