Institution: Queen Mary University of London (QMUL)

Unit of Assessment: A3 (Allied Health Professions, Dentistry, Nursing and Pharmacy)

Title of case study: Topical fluoride therapy to prevent dental caries in children

1. Summary of the impact

The use of fluoride in preventive dentistry was previously fraught with controversy despite numerous primary studies. A series of Cochrane systematic reviews by Queen Mary's Marinho *et al* greatly reduced uncertainty in this field and has been used extensively in the UK (eg Department of Health, Scottish Intercollegiate Guidelines Network) and internationally (eg World Health Organization) since 2002 as strong evidence to support clinical and public health decisions on preventive use of fluorides. The research provided a knowledge framework that enabled decision-makers worldwide to significantly reduce variations in practice and policy, and also reduce burden of dental caries (tooth decay). The research has prompted new, more relevant trials and important advances in systematic review methodology (new statistical approaches for meta-analysis).

2. Underpinning research

Dental caries is one of the most common yet preventable diseases. It is highly prevalent in the UK and worldwide, causing much pain and suffering, which requires extensive treatment resources. In the UK in 2003, 43% and 57% of 12 and 15-year-old children respectively had experienced tooth decay in their permanent teeth, and 16% to 26% of five to 15-year olds reported a toothache in the past 12 months, which represents approximately 1.4 million children in England alone. Dental caries is highly socially patterned, with socio-economically deprived children disproportionately affected. Until recently, there was much uncertainty about the effectiveness of the various fluoride treatments for prevention of dental caries, and about how benefit varied with disease levels and other population and intervention variables.

From 2002, Dr Valeria Marinho and colleagues undertook a series of Cochrane reviews on the main modalities of self- and professionally-applied topical fluoride therapies (TFT) (applying fluoride directly to the teeth) in prevention of caries in children. The reviews addressed the following research questions:

1. What is the efficacy and safety of fluoride toothpastes, mouth rinses, gels and varnishes in preventing dental caries in children and adolescents? [1]
2. Is the efficacy of topical fluorides influenced by background exposure to fluoride sources other than the study options, baseline caries levels, fluoride concentration and application features?
3. Are there differences in efficacy of the various fluoride modalities either used singly (one compared with another) or in combination with each other (primarily fluoride toothpaste plus another topical fluoride modality compared with fluoride toothpaste alone)?
4. Are there differences in efficacy of toothpastes with different fluoride concentrations?
5. What is the risk of developing dental fluorosis (mottling of the tooth enamel) in young children with the use topical fluoride treatments?

These systematic reviews – the most comprehensive and methodologically rigorous on the subject – are based on published and unpublished experimental evidence, mainly from randomised controlled trials, with no language restrictions. They have collated and critiqued over 150 primary studies involving around 70,000 children, using similar methodology and measures of effect, bringing all the evidence together in a consistent way and establishing many findings that individual primary studies were insufficiently powered to show. These Cochrane reviews carefully identified and excluded methodologically flawed studies (which should not inform practice). They involve meta-analyses of all relevant evidence comparing TFT against non-fluoride controls, against each other, and against a combination of TFT. They investigate the comparative effectiveness of TFT as well as the dependence of the caries-preventive effect of fluorides on prognostic features through meta-regression analysis and by direct and indirect comparisons in a network meta-analysis.

The first four reviews (2002 and 2003) [1,2] investigated efficacy of fluoride gels, varnishes, rinses, or toothpastes using placebo or no-treatment controls and examined factors potentially influencing effectiveness. The fifth review (2003) was a summary of the first four, with additional investigations of differences in effectiveness between fluoride modalities based on meta-regression analyses using the treatments as covariates. The sixth review (2004) collated trials of head-to-head comparisons among the four treatments while the seventh review (2004) [3] also involved direct comparisons of these four treatments used in combination versus one form used alone. The eighth review (2010) [5] looked at the relative effectiveness of fluoride toothpastes of different concentrations based on meta-regression analyses and network meta-analysis. The ninth review (2010) [6], which considers evidence from experimental and observational studies, assessed the relationship between the use of topical fluoride, mainly toothpaste, by young children and the risk of developing dental fluorosis. Two ongoing reviews (updating 2007 and 2010) look at the effectiveness of salt fluoridation and of paint-on F solutions in caries prevention/arrest. Thus, new work built on and incorporated earlier work, increasing its current impact. All are published in The Cochrane Library. The methodological research consists of seminal papers on new statistical approaches for incorporating risk of bias assessments in meta-analyses [7], and for new methods for the simultaneous analysis of a network of trials in multiple-treatments meta-analysis [4].

This research is ongoing. New and updated reviews will be published in years to come. The lead researcher is Valeria Marinho (Senior Lecturer, Queen Mary). Co-workers at Queen Mary are Sharea Ijaz (PhD student 2008-) and Dominic Hurst (Clinical Lecturer). Co-workers elsewhere include Aubrey Sheiham (UCL), and editors and co-ordinating editors of the Cochrane Oral Health Group and the Cochrane Collaboration (Clarkson, Worthington, Higgins). The work has been funded/supported by Queen Mary, The University of Manchester, UCL, MRC - UK, DH Cochrane Review Incentive Scheme 2008 - UK, NIHR-UK, CAPES - Brazil, University of Hong Kong, University of Ioannina School of Medicine (Greece).

3. References to the research

Seven papers selected of 15 publications from this stream of research:

1. **Marinho VC**, Higgins JP, Logan S, Sheiham A. Fluoride gels for preventing dental caries in children and adolescents. Cochrane Database of Systematic Reviews 2002a; (2): CD002280.
2. **Marinho VC**, Higgins JP, Sheiham A, Logan S. Fluoride toothpastes for preventing dental caries in children and adolescents. Cochrane Database of Systematic Reviews 2003a; (1): CD002278.
3. **Marinho VC**, Higgins JP, Sheiham A, Logan S. Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus single topical fluoride for preventing dental caries in children and adolescents. Cochrane Database of Systematic Reviews 2004b;(1): CD002781.
4. Salanti G, **Marinho V**, Higgins JP. A case study of multiple-treatments meta-analysis demonstrates that covariates should be considered. *J Clin Epidemiol*. 2009; 62(8):857-64.
5. Walsh T, Worthington HV, Glenny A-M, Appelbe P, **Marinho VCC**, Shi X. Fluoride toothpastes of different concentrations for preventing dental caries in children and adolescents. Cochrane Database of Systematic Reviews 2010 (1): CD007868.
6. Wong MC, Clarkson J, Glenny AM, Lo EC, **Marinho VC**, Tsang BW, Walsh T, Worthington HV. Cochrane reviews on the benefits/risks of fluoride toothpastes. *Journal of Dental Research* 2011; 90: 573-9.
7. Dias S, Welton NJ, **Marinho VCC**, Salanti G, Higgins JPT, Ades AE. Estimation and adjustment of bias in randomised evidence using Mixed Treatment Comparison Meta-analysis. *Journal of Royal Statistical Society A* 2010; 173: 613–629.

4. Details of the impact

4a: Reducing uncertainty in the field. Prior to these systematic reviews, effectiveness estimates for the various fluoride treatments were based on selected published literature of variable quality, reported in broad ranges, and there was no general agreement on the causes of differences in effectiveness. Estimates fell considerably short of a definitive recommendation for topical fluoride as a safe and effective treatment, hence policymakers and practitioners were unsure of the best course of action. On the basis of this work, estimates of TFT efficacy became considerably more

precise (narrower confidence intervals), and causes of differences in effectiveness among treatments could be formally indicated [1-7].

4b: Changing the World Health Organization (WHO) Essential Medicines List. In 2004 the team was invited to produce a summary report based on the results of the Cochrane Fluoride reviews, and this prompted the first major impact of this research. The document directly influenced the WHO Expert Committee on the Selection and Use of Essential Medicines at its 2005 meeting in Geneva [8]. It recommended that sodium fluoride be retained on the Model List of Essential Medicines, but that the description should be changed to "in any appropriate topical formulation". This recommendation is still current, the latest versions are the 17th WHO Essential Medicines List and the 3rd WHO Essential Medicines List for Children updated in March 2011.

4c: Informing and developing clinical practice and dental health policy – nationally and internationally. Findings from this research rapidly influenced policy and practice from professional bodies and health services in UK and internationally. For example, the Queen Mary research underpins numerous recommendations in:

- The influential document 'Delivering Better Oral Health: An Evidence-Based Toolkit' from the UK Department of Health (DH 2009) 1st (2007) and 2nd (2009) editions, which support PCTs and dental teams across the UK in the delivery of preventive approaches in oral health based on the best available research evidence [9];
- The Scottish Intercollegiate Guidelines Network (SIGN) 2005 Guide for the Prevention and Management of Dental Decay in the Pre-school Child [10], and The American Dental Association (ADA) 2007 Evidence-Based Clinical Recommendations on Professionally Applied Topical Fluorides (both still current and in the process of being updated) [11];
- The Guidelines from the Irish Public Dental Service Evidence-based Guidance on the use of Topical Fluorides for Caries Prevention in Children and Adolescents (IPDS 2008) [12], and The European Academy of Paediatric Dentistry Guidelines on the use of Fluorides in Children (EAPD 2009) [13]. Marinho has contributed directly as a consultant and external reviewer in the former and as a presenter, committee member and author in the latter; and
- The Guide to Recommendations for the Use of Fluoride in Brazil: (Ministry of Health 2009) [14], to which Marinho has contributed directly as a consultant/committee member.

The impact of this research on national and cross-national guidelines has been investigated in a recent MSc project [15]. The student looked at the total number of recommendations per type of topical fluoride featuring in the guidelines and at the proportion of Cochrane reviews, non-Cochrane reviews and other types of evidence permeating the guidelines' recommendations. Of 70 recommendations in the guidelines, this research was cited in 57%.

Various recommendations based on the evidence from this research were developed in three jointly organized international meetings (Marinho guest speaker) by the WHO, International Association for Dental Research (IADR), and International Dental Federation (FDI): a Global Consultation on Oral Health through Fluoride in 2006 ((Geneva (Switzerland)/Ferney-Voltaire (France)), a Conference on Oral Health Through Fluoride for China and Southeast Asia in 2007 (Beijing), and the Workshop on Effective Use of Fluoride in Asia in March 2011 (Phan-Nga, Thailand). In particular, the results of the fluoride toothpaste Cochrane reviews played a crucial role in the evidence-based emphasis towards the worldwide promotion of this treatment by these three major international organizations, as demonstrated in their 2007 Beijing Declaration [16] (which followed the 2007 Call to Action to Promote Oral Health meeting); it states that promoting dental health using fluoride, especially in the form of toothpaste, will *"improve quality of life and enhance achievement of the WHO Millennium Development Goals by reducing the high dental disease burden of entire populations, especially children in disadvantaged areas."*

4d: Informing/prompting further research. Following recommendations for further research from our work, many new RCTs, especially fluoride varnish trials, are being or have been carried out in numerous countries, and have been incorporated in a recently published major update of the relevant Cochrane review, which provides even more precise estimates of treatment effects [18].

4e: Advancing research methodology. The methodological work by this team has directly impacted on the development of statistical advances in Cochrane reviews and others, as

demonstrated by their use in the main methodological guides in the field, considered the best resources for conducting systematic reviews: the Cochrane Handbook of Systematic Reviews of Interventions (updated in March 2011) [19], and Marinho's contribution is acknowledged in The Cochrane Collaboration Glossary. The research is also listed within the main publications by the Cochrane Statistical Methods Group [19], not least because the rich data set involving trials for preventing caries in this series of Cochrane fluoride reviews has motivated the development of new methods for network (or "multiple treatment") meta-analysis, particularly around adjusting for bias and accounting for heterogeneity. Also, a new Cochrane Methods group was established in 2010 to take these developments forward Collaboration-wide – the Cochrane Comparing Multiple Interventions Methods Group [19].

5. Sources to corroborate the impact

8. World Health Organisation Expert Committee on the Selection and Use of Essential Medicines recommendation http://whqlibdoc.who.int/hq/2011/a95053_eng.pdf
9. UK Department of Health Guide www.avon.nhs.uk/dental/publications/delivering%20better%20oral%20health.pdf
10. Scottish Intercollegiate Guidelines Network (SIGN) Recommendations www.sign.ac.uk/pdf/sign83.pdf
11. American Dental Association Recommendations www.ada.org/sections/professionalResources/pdfs/report_fluoride.pdf
12. Irish Public Dental Service Evidence based Guidance on the use of Topical Fluoride for caries prevention in children and adolescents www.dentalhealth.ie/download/pdf/full_topf_finaleb.pdf
13. European Academy of Paediatric Dentistry Guidelines on the use of Fluorides in Children www.eapd.gr/dat/82C0BD03/file.pdf
14. Brazilian Ministry of Health Guide to Recommendations for the Use of Fluoride http://cfo.org.br/wp-content/uploads/2010/02/livro_guia_fluoretos.pdf
15. Shahzad S. Use of systematic reviews in clinical practice guidelines: A case study of Fluoride use for caries prevention (Queen Mary University of London, 2010, unpublished MSc thesis).
16. Example of international discussion meeting that drew on this research: WHO IADR FDI Call to Action to Promote Oral Health by using Fluoride www.fdiworldental.org/media/12655/beijing_declaration.pdf
17. Patient leaflets based on this work
    - NHS NorthWest Dental Health patient info on the use of fluoride varnish http://www.northwestdentalhealth.nhs.uk/File.ashx?id=10997
    - GOSH for Children patient info on the use of fluoride toothpaste http://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&source=web&cd=3&ved=0CDoQFjAC&url=http%3A%2F%2Fwww.gosh.nhs.uk%2FEasySiteWeb%2FGatewayLink.aspx%3FalId%3D106870&ei=l56DUompOJKrhQfuiYGQAg&usg=AFQjCNHq-EgC-YOfiBffOq_De5VZEvrwbQ&bvm=bv.56343320,d.d2k
18. **Marinho VC**, Worthington HV, Walsh T, Clarkson JE. Fluoride varnishes for preventing dental caries in children and adolescents. Cochrane Database Syst. Rev. 2013 Jul 11; 7:CD002279. www.ncbi.nlm.nih.gov/pubmed/23846772
19. Cochrane Collaboration publications:
    - Handbook www.igh.org/Cochrane/tools/Ch16_Specialstatistics.pdf
    - Statistical Methods Group http://smg.cochrane.org/search/site/marinho
    - Glossary www.cochrane.org/sites/default/files/uploads/glossary.pdf