

# Translating mouthwash use for gonorrhoea prevention into a public health campaign: identifying current knowledge and research gaps

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**Abstract.** The gonorrhoea rate among gay and bisexual men who have sex with men (MSM) has been increasing rapidly in many Western countries. Furthermore, gonorrhoea is becoming increasingly resistant to antibiotics and only limited options remain for treatment. Recent evidence suggests that the oropharynx may play an important role in gonorrhoea transmission. It is hypothesised that reducing the prevalence of oropharyngeal gonorrhoea will also reduce the population incidence of gonorrhoea. Mouthwash has been proposed as a novel non-antibiotic intervention to prevent oropharyngeal gonorrhoea; hence, reducing the probability of antibiotic resistance developing. However, its efficacy is yet to be confirmed by a randomised controlled trial – the findings of which will be available in 2019. If the trial shows mouthwash is effective in preventing gonorrhoea, this finding could potentially be translated into a public health campaign to increase the mouthwash use in the MSM population. This article summarises the current evidence of the effectiveness of mouthwash against gonorrhoea and discusses the potential literature gaps before implementing the mouthwash intervention at a population level.

**Additional keywords:** gay men, intervention, men who have sex with men, *Neisseria gonorrhoeae*, prevention, sexually transmitted diseases, sexually transmissible infections.

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## Introduction

Gonorrhoea is increasing at an alarming rate among gay and bisexual men who have sex with men (MSM) not only in Australia but also in many western countries.<sup>1–4</sup> The rise of antimicrobial resistance in *Neisseria gonorrhoeae* in recent years is of particular concern.<sup>5</sup> Recently, the first cases of *Neisseria gonorrhoeae* resistant to both ceftriaxone and azithromycin were found in Australia<sup>6</sup> and the UK, and herald the prospect of gonorrhoea becoming substantially more difficult to treat.<sup>7</sup> Clinical trials on three new antibiotics to treat gonorrhoea (solithromycin, zoliflodacin and gepotidacin) are currently underway.<sup>8</sup> A phase II clinical trial has demonstrated that the microbiologic cure rate of a single dose of zoliflodacin for anorectal gonorrhoea was 100% and for urogenital/cervical gonorrhoea, it was 96%; however, it was less effective for oropharyngeal gonorrhoea (50–82%).<sup>9</sup>

The control of oropharyngeal gonorrhoea is complicated because it has a relatively short duration of infection, up to 3–4 months.<sup>10,11</sup> Individuals with oropharyngeal gonorrhoea are almost always asymptomatic;<sup>12</sup> therefore, the current recommended annual screening would have missed most oropharyngeal cases. The importance of oropharyngeal

gonorrhoea has been highlighted in a recent hypothesis and mathematical models that suggest it may play an important role in transmission and control of gonorrhoea in MSM.<sup>13–15</sup> Oral sex is common among MSM. MSM can acquire oropharyngeal gonorrhoea from condomless oral sex (fellatio),<sup>16</sup> but condom use for oral sex among MSM is relatively low.<sup>17</sup> A US study surveyed 871 sexually active MSM and found that only 9% used condoms for oral sex consistently in the last 12 months.<sup>18</sup> Recent qualitative research has indicated that men do not like the loss of sensation or the taste of condoms during oral sex and thus they are not willing to use condoms for fellatio.<sup>19,20</sup> Nevertheless, condomless anal sex has also been increasing among MSM over the last few years in the era of pre-exposure prophylaxis (PrEP) for HIV.<sup>3,21</sup> In addition, a mathematical model has predicted that gonorrhoea cannot be eliminated, even in a scenario with 100% condom use for anal sex.<sup>22</sup> A recent hypothesis and other data suggest that oropharyngeal gonorrhoea may be transmitted via kissing in addition to condomless fellatio and possibly rimming (i.e. oro-anal contact).<sup>15,23–29</sup> In the context of this new data and the falling rate of condom use, novel interventions for gonorrhoea prevention that targets the oropharynx are required if

successful control is to be realised. It has been suggested that an antibacterial mouthwash could be used to prevent oropharyngeal gonorrhoea.<sup>30,31</sup> If mouthwash is proven to be effective against *Neisseria gonorrhoeae*, this can be translated into an important public health campaign to increase mouthwash use at a population level. However, there are several unknown factors that need to be solved if mouthwash is to be implemented for gonorrhoea prevention. The aim of this paper is to: (1) discuss the current knowledge and understanding of mouthwash use for gonorrhoea prevention; and (2) identify what future studies are required before translating mouthwash use as a public health campaign to prevent gonorrhoea at a population level.

### Current evidence on mouthwash to prevent oral diseases

Clinical studies have demonstrated that the use of antibacterial mouthwashes can effectively prevent plaque and gingivitis.<sup>32–34</sup> Addy *et al.* (1991) conducted an observational study on 10 healthy young adults and showed that there was a large reduction in bacterial counts in saliva for up to 7 h after rinsing with chlorhexidine-containing mouthwashes.<sup>35</sup> Other studies have confirmed these findings and shown a significant reduction in levels of aerobic and anaerobic bacteria in both saliva and mucosal samples after using antimicrobial mouthwash.<sup>36,37</sup>

The antibacterial properties of mouthwash prompted investigators to propose more than 30 years ago that mouthwash be used for post-exposure prophylaxis for STIs, particularly among sex workers.<sup>38–40</sup> Recent evidence is consistent with this proposition because high bacterial loads of *Neisseria gonorrhoeae* bacterial are present in the saliva among men with oropharyngeal gonorrhoea.<sup>27</sup> Therefore, it was hypothesised that the use of mouthwash can effectively reduce the bacterial load of *Neisseria gonorrhoeae* in saliva and thus prevent ongoing transmission. However, until recently, there had been very limited scientific evidence to support the proposition that mouthwash may prevent an STI. Recently, an *in vitro* study has demonstrated that two alcohol-containing Listerine® products can inhibit the growth of *Neisseria gonorrhoeae* to less than 10<sup>2</sup> colony forming units (CFU) per mL.<sup>30</sup> Another *in vitro* study has shown that Chlorhexidine 0.2% mouthwash can also inhibit the growth of *Neisseria gonorrhoeae* to less than 10<sup>2</sup> CFU per mL, and authors revealed the inhibitory effect is stronger with a longer exposure time.<sup>41</sup> Both *in vitro* studies used phosphate buffered saline as a control and displayed no inhibitory effect in the control group.

To date, there has been only one published randomised controlled trial (RCT) examining the effect of mouthwash against *Neisseria gonorrhoeae*.<sup>30</sup> This RCT randomised 58 MSM with untreated oropharyngeal gonorrhoea into either the mouthwash or saline group, and participants were instructed to rinse and gargle the allocated solution for 60 s. Results showed almost half (48%) of MSM cleared the infection in the mouthwash group, compared with only 16% in the saline group ( $P = 0.013$ ). The clearance effect is more profound at the tonsillar fossae compared with the posterior oropharynx, suggesting it is important for mouthwash to reach the posterior oropharynx.

### A novel intervention on mouthwash use to prevent oropharyngeal gonorrhoea

Based on the findings from previous *in vitro* studies and the single RCT, it has been suggested that mouthwash may lead to a novel intervention preventing gonorrhoea in the oropharynx,<sup>30,41</sup> and findings from the OMEGA (Oral Mouthwash use to Eradicate GonorrhoeA) study will answer the question about whether this novel approach may work.<sup>31</sup> In brief, the OMEGA trial is a large multicentre double-blind RCT conducted in Australia, which has recently completed. The OMEGA trial recruited more than 500 MSM in Melbourne and Sydney and examined whether daily use of mouthwash over a 3-month period can effectively prevent gonorrhoea in the oropharynx. The trial used two different types of alcohol-free mouthwash – one active mouthwash, which has an inhibitory effect against *Neisseria gonorrhoeae* *in vitro*, and one control mouthwash, which has no inhibitory effect against *Neisseria gonorrhoeae*, which aimed to examine whether daily use of active mouthwash for 3 months could prevent oropharyngeal gonorrhoea. It is anticipated that the results of the OMEGA trial will be available in 2019.

### A potential public health campaign on mouthwash use to prevent and control gonorrhoea

If the results from the OMEGA trial show that daily use of the 'active' mouthwash can prevent oropharyngeal gonorrhoea in MSM, it would be reasonable to translate this finding into a public health campaign that recommends daily mouthwash use as a preventive strategy for oropharyngeal gonorrhoea. Increasing mouthwash use in the community could potentially reduce the overall incidence of gonorrhoea at a population level and thus reduce the potential for resistant strains to develop. Daily mouthwash use has also been reported to be an acceptable and easy intervention for gonorrhoea among the MSM population.<sup>19,20,42</sup> A mathematical model has predicted that a 50% coverage of daily mouthwash use that had the effect of increasing the daily untreated clearance of gonorrhoea in the oropharynx would result in a seven-fold reduction in the prevalence of gonorrhoea at all sites in MSM.<sup>15</sup> However, there are several research questions that need to be answered before recommending or implementing mouthwash for gonorrhoea prevention if it were shown to work in the OMEGA trial.<sup>13,31,43</sup>

To date, the recommendations about mouthwash use have been for the prevention of oral diseases such as gingivitis and not gonorrhoea prevention. Based on the clinical trial conducted by Ross *et al.* (1993), the recommendation of mouthwash for preventing gingivitis is to use it twice daily as a mouthwash rinse for 30 s.<sup>44</sup> There are also no recommendations about how to use a mouthwash to prevent gonorrhoea except from the OMEGA trial (i.e. rinse and gargle 20 mL of mouthwash for 60 s every day).<sup>31</sup>

It is likely that the use of mouthwash to prevent gonorrhoea will be different to gingivitis; for example, the site of the required action is likely to be different. Oropharyngeal *Neisseria gonorrhoeae* is primarily detected in both the tonsils and posterior oropharynx by nucleic acid amplification test (NAAT); however, a small proportion (6–10%) of infection is only detected at either the tonsils or the posterior oropharynx.<sup>45</sup> If mouthwash is effective in preventing gonorrhoea, it is important

to have specified guidelines for use that enable the mouthwash to reach both the tonsils and posterior oropharynx. How this is best achieved is not known.

#### *Which mouthwash works?*

Another important question is to identify the types of mouthwash that have inhibitory effects against *Neisseria gonorrhoeae*. To date, only one small clinical trial has demonstrated Listerine® Cool Mint (with 21.6% alcohol) could inhibit the growth of *Neisseria gonorrhoeae*,<sup>30</sup> and the OMEGA trial used alcohol-free mouthwashes (product names withheld until publication).<sup>31</sup> The alcohol-free mouthwash in the intervention arm of the OMEGA trial has been tested *in vitro* and has been found that it could inhibit the growth of *Neisseria gonorrhoeae* (D. A. Williamson, unpubl. data). This suggests that alcohol is not the key protective factor against *Neisseria gonorrhoeae*. Nevertheless, there are more than 100 different commercial mouthwash products in the market. Further laboratory testings will be required to identify which mouthwash has an inhibitory effect against *Neisseria gonorrhoeae*.

#### *Mouthwash dosing*

The OMEGA trial recommends using mouthwash at least once a day<sup>31</sup> and it is currently the only clinical trial examining the effectiveness of mouthwash against oropharyngeal gonorrhoea. If mouthwashes can be used as prophylaxis for gonorrhoea, it is hypothesised mouthwash can also be taken in several other ways rather than daily and this concept is similar to PrEP.<sup>46,47</sup> Further research and trials are required to explore the role and effectiveness if mouthwash is taken periodically or during episodic risk-taking (e.g. after sexual exposure, overseas travel).

#### *How to use a mouthwash*

The way mouthwash is used may also influence its effect. If it is diluted, this may also reduce the antibacterial effect against *Neisseria gonorrhoeae*. Some commercial mouthwashes, particularly those alcohol-containing mouthwashes, cause a burning sensation, which creates discomfort. Although none of the manufacturers recommend their consumers dilute their mouthwash for best use (Table 1), it is estimated that a small proportion of individuals (7%) in the general population in the UK dilute their mouthwash for use.<sup>48</sup> A small pilot study on 10 MSM showed no individual (0%) diluted their mouthwash.<sup>42</sup>

The way mouthwash is used will also influence what areas it reaches. Most of the manufacturers recommend the users rinse the mouthwash solution thoroughly so that the solution can cover the entire oral cavity and only a few manufacturers recommend the users both rinse and gargle the solution (Table 1). The site of oropharyngeal gonorrhoea infection is often at the posterior oropharynx;<sup>45</sup> and therefore, it is reasonably hypothesised that the act of gargling would be important and required for the mouthwash to reach the back of the oropharynx to clear gonorrhoea infection. Lin and Raman (2012) conducted a pilot study on 10 individuals assessing the efficacy of three different methods (oral rinse 15 mL for 30 s, oral gargle 15 mL for 30 s and oral spray four squirts) to treat a

sore throat.<sup>49</sup> The authors examined the visualisation of food dye in seven areas of the oral cavity, this includes the uvula, tongue, posterior pharyngeal wall, soft palate, posterior tonsillar pillar, anterior tonsillar pillar and tonsils (Fig. 1). Results showed that both oral gargle and oral spray have similar efficacy in reaching the oropharynx and both were better than oral rinse. This highlights the importance of oral gargle or oral spray if mouthwash is used for preventing gonorrhoea. This is also consistent with a recent study on 20 individuals in Melbourne.<sup>50</sup> Across all three different methods, most people prefer oral spray followed by oral rinse then oral gargle.<sup>50</sup> Furthermore, other formulations of mouthwash such as tablets and strips should also be explored because some people may have difficulty in gargling a mouthwash, especially individuals with very sensitive gag reflexes. Gargling was reported as the least preferred method, described as 'more difficult' and 'uncomfortable' compared with rinse and spray that are 'quick and easy'.<sup>50</sup>

The optimal frequency, time and volume of mouthwash use are also not known. Most mouthwashes are recommended two times a day and do not specify the maximum number of times per day, except Biotène®, which recommends not using their product more than five times a day. Table 2 shows the proportion of daily mouthwash use varies in different settings and populations, ranging from 13% among university students in Italy<sup>54</sup> to 64% among orthodontic patients in Malaysia.<sup>60</sup> Most mouthwash users use mouthwash to prevent bad breath or avoid tooth decay.<sup>48,57</sup> There are very few studies examining mouthwash use in specific populations that are stratified by sexual risk. One study in Melbourne reported 32% of MSM used mouthwash daily.<sup>61</sup> Another study reported 61% of female sex workers (FSWs) in Melbourne used mouthwash daily.<sup>63</sup>

Mouthwash use also varies by different sociodemographic characteristics. Several studies have found that more females use mouthwash than males.<sup>55,57,58</sup> Mouthwash use also varies by age, but findings from published studies are not consistent and the relationship is not fully understood; for example, Macfarlane *et al.* found that the proportion of mouthwash use decreases with increasing age in the general population in Scotland.<sup>58</sup> Phillips *et al.*, however, found that the proportion of mouthwash use increases with increasing age among MSM in Melbourne.<sup>64</sup> Furthermore, Sämer *et al.* did not find any significant association between age and mouthwash use in the Swedish population.<sup>57</sup> Phillips *et al.* have further demonstrated that mouthwash use is not associated with an increasing number of kissing or oral sex partners among MSM.<sup>64</sup> Further research is required to understand why mouthwash use is not common among young adults, especially young MSM, because they are at a higher risk of gonorrhoea.<sup>65</sup>

#### *Optimal time of mouthwash use*

The small RCT and the OMEGA trial recommended participants to use mouthwash for 60 s, although most commercial mouthwashes only recommend use for 30 s (Table 1). One study found that rinsing for 30 s is sufficient for the mouthwash to prevent plaque compared with 60 and 90 s rinsing periods.<sup>66</sup> However, the optimal time of mouthwash use for gonorrhoea prevention is still unknown.

**Table 1. Manufacturer's recommendations for commercial mouthwash use**  
 '–' represents the information is not stated by the manufacturer

Brand	Occasions	Volume (mL)	Time (s)	Recommendation for mouthwash use	Other warnings
Aesop	Morning and evening after brushing, or as required Twice daily	10–20	30	Gargle then expel	–
All Smiles (Woolworths <sup>A</sup> )	–	20	30	Rinse and gargle	Undiluted Do not swallow Use up to five times per day Do not swallow
Biotène	–	15	30	Rinse thoroughly	–
Coles Mint Fresh <sup>A</sup>	Twice a day, morning and night after brushing and flossing	20	30	Rinse and gargle undiluted mouthwash	–
Colgate	Twice a day	20	30	Rinse mouth thoroughly, gargle and expel	Do not dilute
Dentitex (Aldi <sup>A</sup> )	Twice daily	20	30	After brushing and flossing rinse, then gargle	Do not swallow
Denty1	Use twice daily	Half fill cap	30	Shake to one colour - Rinse 30 s, gargle	Do not dilute For best results, do not eat or drink for 30 min after rinsing
Grant's Xylitol Natural	After brushing	–	20–30	After brushing, swirl or gargle around your mouth	–
Listerine	Morning and evening	20	30	Rinse undiluted solution after brushing and flossing	Do not eat or drink for 30 min after rinsing
Listerine Bright White	Twice daily	10	60	After brushing and flossing, rinse undiluted	Do not swallow
Oral B	Twice a day	20	30	Vigorously swish the rinse in your mouth	Do not eat or drink for 30 min after rinsing
Oral B 3D White Luxe	Twice a day after brushing	10	60	Vigorously swish the rinse between your teeth	Do not swallow
Oral7 Moisturising Mouthwash	2–3 times a day	Capful	30	Rinse mouth after brushing	Do not eat or drink for 30 min after rinsing Best not to dilute, but can be to a 50% solution if taste is too strong
Oralube Saliva Substitute	As needed	1–2 sprays	–	Spray directed into the back of the mouth and tongue	–
Sensodyne	Twice daily after brushing	10	60	Rinse	Do not swallow Do not rinse with water
Ultrafresh Coolmint Breath Freshener Spray	As needed	1–2 sprays	–	Direct spray nozzle into your mouth and push pump down	–
White Glo Charcoal Mouthwash	1 or 2 times daily	20	30	Rinse the mouth	Use undiluted Do not swallow and do not rinse after use

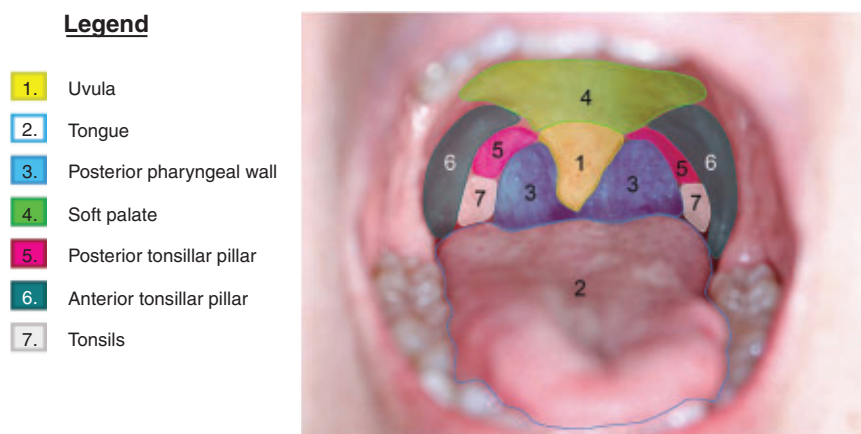
<sup>A</sup>Woolworths and Coles are the two largest Australian supermarkets. Aldi is a Germany brand supermarket in Australia.

**Table 2. A summary of mouthwash use in different populations**  
N/A, not applicable

Reference	Study period	Location	Study populations	Age (years)	Gender	Measurement period	Mouthwash use, n/N (%)
Benjamin <i>et al.</i> <sup>51</sup>	N/A	Nairobi, Kenya	Medical and dental students	N/A	Males (46%), females (54%)	Daily	23/80 (28.8)
Da'ameh <i>et al.</i> <sup>52</sup>	N/A	Irbid, Jordan	Orthodontic patients	9–37	Males (30%), females (70%)	Daily	63/243 (25.9)
Neamatollahi and Ebrahimi <sup>53</sup>	2006–07	Iran	University students	≥18	Males (32%), females (68%)	Daily	372/1736 (21.4)
Rimondini <i>et al.</i> <sup>54</sup>	2001	Italy	University students	20–26	Males (52%), females (48%)	Daily	26/202 (12.8)
Ashwath <i>et al.</i> <sup>55</sup>	N/A	Chennai, India	Dental college undergraduate students	18–22	Males (46%), females (54%)	Regularly <sup>A</sup>	89/259 (34.4)
Ellershaw and Spencer <sup>56</sup>	2004–06	Australia	General population of Australia – National Survey data	≥18	Males (40%), females (60%)	In the previous week	4833/12392 (39.0)
Sämer <i>et al.</i> <sup>57</sup>	2009	Västra Götaland, Sweden	General population	17–94	Males (55%), females (65%)	Daily	198/422 (46.9)
Wirth <i>et al.</i> <sup>48</sup>	July – August 2009, and July – November 2011	Grampian Region, Scotland	General population	25–96	Males (38%), females (62%)	Ever	61/73 (83.6)
Macfarlane <i>et al.</i> <sup>58</sup>	October 2009 – January 2010	Grampian, Scotland	General population of Scotland	≥25	Males (52%), females (48%)	Daily	646/2575 (25.1)
Mitha <i>et al.</i> <sup>59</sup>	July – September 2013	Malaysia	Adults	≥18	Males (39%), females (61%)	Ever	950/2575 (36.9)
Lee <i>et al.</i> <sup>60</sup>	March – April 2015	Bandar Baru Bangi, Malaysia	Fixed orthodontic patients	Mean age 21.6 ± 5.8	Males (29%), females (71%)	Daily	133/400 (33.3)
Chow <i>et al.</i> <sup>61</sup>	March – June 2015	Melbourne, Australia	Men who have sex with men	≥18	Males (100%)	Daily	168/261 (64.4)
Khraisat <i>et al.</i> <sup>62</sup>	April – August 2015	Az-Zarqa, Jordan	Patients attending orthodontic clinic	13–30	Males (50%), females (50%)	Daily	265/823 (32.2)
Zappulla <i>et al.</i> <sup>63</sup>	September 2017 – March 2018	Melbourne, Australia	Female sex workers	≥18	Females (100%)	Ever	652/823 (79.2)
						During orthodontic treatment	190/582 (32.6)
						Daily	109/179 (60.9)
						Ever	163/179 (91.1)

<sup>A</sup>The study asked 'Do you use mouthwash regularly?'; however, it did not define the term 'regularly'.





**Fig. 1.** Anatomy of the oral cavity.

The optimal volume of mouthwash use is also important to determine whether it provides sufficient coverage to inhibit the growth of *Neisseria gonorrhoeae* in the oropharyngeal area. A small volume of mouthwash may be difficult to gargle,<sup>67</sup> but a large volume of mouthwash may also be difficult to gargle due to the creation of bubbling from the mouthwash. The manufacturer's recommendation of the volume of mouthwash for each use varies across different brands, ranging from 10 mL to 20 mL (Table 1). One survey conducted in Scotland estimated that about 89% of adults rinsed with one mouthful of mouthwash (i.e. a mouthwash was defined as 20 mL in the survey).<sup>48</sup> Keukenmeester *et al.* compared the different volumes of mouthwash for rinsing and they concluded that 15 mL of mouthwash appears to be the most acceptable and comfortable volume for each use.<sup>68</sup>

#### *Mouthwash use after sexual exposure*

Harm-reduction programs recommend FSWs to use mouthwash after performing fellatio with their clients but not to brush their teeth.<sup>40</sup> Currently, it is still unclear whether mouthwash should be used straight after sexual exposure to maximise its effectiveness. A small pilot study has found that most MSM use mouthwash as part of their daily routine dental care, but rarely before or after oral sex.<sup>42</sup> This contrasts with FSWs where mouthwash is mainly used before and after each client.<sup>63</sup> Further studies examining the changes in oral microbiome before and after mouthwash use will be required to inform the safety of mouthwash use in relation to sexual exposure.

#### **Modes of delivery of public health campaign**

The correct modes of delivery of the public health campaign need to be identified and explored to maximise the effectiveness of the campaign and also increase the coverage of the targeted population. Evidence has shown that sexual health messages are well delivered to the MSM population through social marketing approaches such as advertising material on the websites, in the media, at public events and via dating websites.<sup>69</sup> Digital media interventions using social media platforms and smartphone dating applications have also been found to be effective in promoting sexual health messages, particularly to young

adults.<sup>70,71</sup> As with other public health interventions such as the human papillomavirus vaccine or HIV PrEP, the monitoring and roll out of mouthwash use intervention will require similar long-term surveillance and measurement of the intervention in the targeted population at a population level.

#### **Other concerns**

There have been concerns about whether alcohol-containing mouthwash would increase the risk of oropharyngeal cancer.<sup>72,73</sup> To date, the concentration of alcohol in commercial mouthwashes varies, ranging from 5% to 26%.<sup>73</sup> Gandini *et al.* (2012) conducted a meta-analysis and concluded that there was no association between oral cancer and frequent mouthwash users, including those who use mouthwash up to three times per day.<sup>74</sup> Oral cancer is more likely to be associated with poor oral hygiene.<sup>75,76</sup> Moreover, there has been no effect on the breath alcohol levels after using the alcohol-containing mouthwash.<sup>77</sup>

#### **Conclusion**

Gonorrhoea is on the rise in many Western countries and several health organisations have indicated that antimicrobial resistance to *Neisseria gonorrhoeae* is a major public health threat globally. Oropharyngeal gonorrhoea is common and may play an important role in gonorrhoea transmission in MSM. Mouthwash has been proposed as a novel preventive strategy for gonorrhoea in the OMEGA trial, but the results of the OMEGA trial will not be available until 2019. If these and other studies show it is effective, mouthwash use can be translated into a public health campaign for gonorrhoea prevention and control. However, several questions remain and need to be solved before rolling it out as a community intervention to maximise the effectiveness of the campaign.

#### **Conflicts of interest**

The authors declare no conflicts of interest.

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