

**Treatment Patterns for  
External Genital Warts in Australia, 1997**

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## ABSTRACT

**Objective:** To describe the current treatment patterns for external genital warts employed by Australian doctors in 1997.

**Methods:** Information regarding treatment modalities employed, maximum number of visits for each treatment type and referral patterns was obtained from a postal survey of general practitioners (GPs) and a telephone survey of sexual health clinic doctors across Australia.

**Results:** Cryotherapy is the most common first line topical therapy employed by GPs for the treatment of external genital warts for both males (51%) and females (41%). The second most common treatment modality employed is podophyllin (29% and 33% respectively). Podophyllotoxin is not used extensively by GPs in either male (5%) or female (6%) patients. 'Other therapies' are rarely used as first line therapy (3-5%). Cryotherapy and podophyllin involve at most, 3 to 4 visits to the clinic, although podophyllin requires on average 0.6 of a visit more than cryotherapy. Podophyllotoxin requires on average 2 to 3 visits, substantially less than podophyllin ( $p < 0.05$ ).

In sexual health clinics, cryotherapy is the most common first and second line treatment employed for the management of external genital warts in both males (63% and 44% respectively) and females (53% and 51% respectively). Unlike GPs, sexual health clinic doctors use podophyllotoxin much more frequently both as first and second line treatments in both male and female patients. Referrals are made much less commonly representing only 3% of first line therapy and 6-11% of second line therapy selected.

**Discussion:** Cryotherapy and topical podophyllin represent the vast bulk of first-line treatments in Australia for genital warts particularly in the General Practice sector. Podophyllotoxin certainly plays a bigger part in the treatment practices in the STD clinics particularly in the management of persistent warts. More aggressive therapies are uncommonly employed in either sectors.

# TABLE OF CONTENTS

<b>Introduction</b>	<b>1</b>
<b>Methods</b>	<b>2</b>
<b>Results</b>	<b>3</b>
<b>Discussion</b>	<b>7</b>
<b>References</b>	<b>11</b>
<b>Appendix</b>	<b>12</b>
<b>List of Tables</b>	
<b>Table 1</b>	<b>3</b>
<b>Table 2</b>	<b>4</b>
<b>Table 3</b>	<b>5</b>
<b>Table 4</b>	<b>6</b>
<b>Table 5</b>	<b>7</b>

# Treatment Patterns for External Genital Warts in Australia, 1997

## Introduction

Genital warts are increasing in incidence worldwide. They are one of the most common sexually transmitted diseases (STDs) in the United States, United Kingdom and New Zealand (1,2,3). In the United States it has been estimated that approximately 1 million new cases of infection occur per year (1), with clinic visits for genital warts increasing 4.5 fold between 1966 and 1984 in some areas of the country (4). In New Zealand genital warts represented 17.9% of new patients presenting to sexual health clinics in 1993, with a seven-fold increase in attendances from 1977 through to 1993 (2).

Genital warts are not a notifiable disease in Australia and accurate incidence figures are lacking. It has, however, been estimated that the prevalence of genital warts in adults is approximately 1-2% with the majority of cases affecting sexually active young adults.

With respect to clinical management of genital warts it has been estimated that in Australia, the majority of individuals present to their general practitioner (GP) (6). One source of information regarding the prevalence of genital wart related general practice visits is the Australian Morbidity Treatment Survey (AMTS). AMTS was conducted in 1990/91 by the Family Medical Research Unit at the University of Sydney, involving a randomly selected group of 495 general practitioners who recorded the reasons for encounter and management of all patients seen during two one week periods, 6 months apart. Details with respect to the prevalence of genital warts in General Practice are summarised as follows: genital warts are a reason for presentation in approximately 1/1000 consultations; and the average GP sees 120 patients per week. Using these data, we estimated that the average GP sees approximately 6 patients with genital warts per year (6).

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Some patients may initially present to a family planning or STD clinic. In New Zealand, the majority of patients presenting to an STD clinic are self-referred, with only 6.4% being referred by a doctor in 1993 (3).

However, there is no published data available regarding the current clinical practices of this disease in Australian clinics. In addition, management practices are most likely to vary from physician to physician since there is no specific antiviral therapy available and no one current method of treatment is superior to the others (2). The aim of this paper is to describe the utilisation of different treatments for external genital warts used by medical practitioners.

## Methods

The study was a General Practice Division (GPD)-based, GP survey of treatment practices of external genital warts. There are a total of 119 GPDs in Australia, each containing anywhere between 100 to 300 registered GPs, representing approximately 70% of all Australian GPs (6). We randomly selected one to two GPDs per state which depicted a reasonably representative population of Australian GPs. A formal request was made to the chief executive of each GPD chosen who agreed to the mail out of questionnaires to every GP registered in their division. The sample size calculated was designed to achieve confidence limits of 5 per cent around the estimate of GPs treating patients with genital warts at the 95 percent level, assuming that 80 per cent of GPs managed a case of genital warts in the past month. This sample size was calculated to be 1200, allowing for an expected response rate of 20 per cent

The study population included those GPs who were registered with any of the following GPD as of November, 1996: Fairfield (NSW), Central Coast (NSW), Greater South East Melbourne (VIC), Geelong (VIC), Logan Area (QLD), Sunshine Coast (QLD), Adelaide Northern (SA) and Osborne (WA). A total of 1600 questionnaires were mailed out in December, 1996 to the eight GPDs. Unfortunately mailing of the questionnaire from the Southern Tasmanian GPD did not occur until February, 1997, so this division has been excluded from the analysis.

The questionnaire asked each GP to: 1) estimate the number of male and female cases of external genital warts that they manage per month; 2) to state their management practice of external genital warts for both sexes that they employ for both first line and, second line therapy (if the first line therapy failed) and the treatment of recurrent warts (warts which have responded to initial therapy but then later reappeared); 3) to state their referral rates; and 4) to indicate the approximate maximum number of visits to the clinic required to complete each course of treatment. If the GP had indicated referral as a treatment type, they were asked to document which type of specialist. If the GP had indicated 'other' as a treatment type they were asked to notate the treatment type.

In addition, we randomly selected and interviewed by telephone 13 sexual health clinics in Victoria, New South Wales, South Australia, Queensland and Western Australia. All clinicians completed the same questionnaire.

Data were analysed using EPI INFO version 6.1. The weighted mean percentage was calculated for each treatment type, and their respective 95 per cent confidence intervals. Males and females were analysed separately, as were the GPDs as we expected some differences in treatment and referral patterns.

## Results

A total of 1600 questionnaires were mailed out and 324 were returned and analysed by the end of February 1997. The response rate was 20.3%. Response rates by GPD are summarised in Appendix 1. There was no second mail out.

The GPs who responded to our questionnaire treat on average 0.9 cases of male genital warts and 1.1 cases of female genital warts during the course of an average month.

### Treatment patterns

Table 1 suggests that the most common first line topical therapy for non-cervical genital warts is cryotherapy for both males (51%) and females (41%), and the second most common is podophyllin (29% and 33% respectively). Podophyllotoxin is not used extensively in either male (5%) or female (6%) patients. 'Other therapies' are rarely used as first line therapy (3-5%). The types of 'other' treatment indicated and their relative frequencies are summarised in Table 2.

Table 1  
Treatment patterns (%) for external genital warts in both men and women by GPs who responded to the survey: weighted average percentages of responses (95%CI).

<b>Males</b>	<b>First line therapy (95%CI)</b>	<b>Second line therapy (95%CI)</b>	<b>Treatment of recurrent warts (95%CI)</b>
Nil	1.4 (0-2.0)	0.8 (0-1.8)	2.0 (0.4-3.6)
Cryotherapy	50.5 (45.2-56.8)	23.2 (18.7-27.7)	33.0 (27.9-38.1)
Podophyllin	28.5 (24.0-33.2)	13.4 (9.9-16.9)	14.2 (10.5-17.9)
Podophyllotoxin	4.5 (2.3-6.7)	5.3 (2.9-7.7)	3.0 (1.2-4.8)
Referral	10.5 (7.4-13.6)	50.6 (45.1-56.1)	42.3 (36.6-48.0)
Other	4.6 (1.5-7.7)	6.5 (3.8-9.2)	5.5 (3.0-8.0)
<b>Females</b>	<b>First line therapy (95%CI)</b>	<b>Second line therapy (95%CI)</b>	<b>Treatment of recurrent warts (95%CI)</b>
Nil	1.8 (0.6-3.0)	0.7 (0-1.7)	1.8 (0.2-3.4)
Cryotherapy	41.3 (36.4-46.2)	20.8 (16.5-25.1)	24.5 (19.8-29.2)
Podophyllin	32.5 (27.6-37.4)	11.6 (8.3-14.9)	15.9 (12.0-19.8)
Podophyllotoxin	5.5 (3.1-7.9)	4.2 (2.0-6.4)	4.3 (2.1-6.5)
Referral	16 (12.3-19.7)	58.2 (52.7-63.7)	50.0 (44.3-55.7)
Other	3.2 (1.4-5.0)	4.3 (2.1-6.5)	3.8 (1.8-5.8)

**Table 2**  
**Summary of 'other' treatment methods selected**

Males	Percentage of 'other' treatment
Electrocautery or diathermy	56
Trichloroacetic acid (TCA)	23
High dose Cimetidine	8
Aiclovir	5
Combination therapy (ie. cryotherapy & podophyllin)	5
Salicylic acid (30-40%)	3
Females	Percentage of 'other' treatment
Electrocautery or diathermy	39
Trichloroacetic acid (TCA)	32
High dose Cimetidine	11
Aiclovir	4
Combination therapy (ie. cryotherapy & podophyllin)	10
Naturopathy	4

When the first-line treatment patterns are analysed according to the number of cases managed per month we found for male patients that those GPs who treated more than one case per month are 30% more likely to use cryotherapy and 50% less likely to refer than those GPs who managed less than one case per month. For female patients the differences are less marked.

The most popular second line treatment for warts that failed to respond to the first line therapy for both males and females is referral to a specialist (51% and 58% respectively) (Table 1), with cryotherapy being the next most common option selected.

Referral remains the most common treatment option for persistent warts when each of the first line treatments are analysed separately except for when 'other' treatment is chosen as the first option. Here the GP is most likely to select 'other' treatment for persistent warts in both males and females.

The selected treatment option of recurrent warts again in both males and females is referral (42% and 50% respectively) although cryotherapy is a close second especially in males (33%).

### **Treatment patterns by General Practice Division**

Differences in treatment patterns are noted between the different GPDs although these are not significant ( $p > 0.05$ ).

### **Number of visits to GP by treatment type**

Table 3 shows the average maximum number of visits per treatment. That is to say the maximum time for which the average GP would continue therapy before taking some other option. Cryotherapy and podophyllin would at most involve 3 to 4 visits to the clinic, although podophyllin requires on average 0.6 of a visit more than cryotherapy. Podophyllotoxin would at most require

on average 2 to 3 visits, substantially less than podophyllin ( $p < 0.05$ ). There is little difference between men and women ( $p > 0.05$ ).

**Table 3**  
**Maximum number of visits required (95%CI) for each treatment type used in the management of external genital warts in both men and women as indicated by GPs who responded to the survey**

Treatment type	First line therapy (95%CI)	Second line therapy (95%CI)	Treatment of recurrent warts (95%CI)
Nil	1.3 (0.9-1.9)	1.4 (0.3-3.1)	1.5 (1.0-2.2)
Cryotherapy	3.4 (3.1-3.8)	3.3 (2.9-3.7)	3.6 (3.2-4.0)
Podophyllin	3.9 (3.5-4.3)	3.9 (3.3-4.5)	4.2 (3.6-4.8)
Podophyllotoxin	2.8 (2.1-3.0)	2.5 (2.0-3.0)	3.0 (1.9-3.1)
Referral	1.0 (0.9-1.1)	1.0 (0.98-1.02)	1.0 (0.96-1.04)
Other	2.7 (2.0-3.4)	2.5 (2.0-3.0)	2.8 (2.1-3.5)

For persistent warts, the maximum number of visits for each treatment type either reduced slightly or remained static.

Where warts recur, the maximum number of visits for both cryotherapy and podophyllin is 0.2 more than for the original treatment, while those for podophyllotoxin, referral and 'other' are the same as for the original treatment. Again there is little difference between men and women ( $p > 0.05$ ).

### Referrals made by GPs

Of those GPs who refer male patients, most refer either to a urologist (42%) or a sexual health clinic (39%). Most female patients are referred to a Gynaecologist (68%). Other specialists referred to include Dermatologists, General Surgeons, Infectious Disease Physicians and Laser Centres. Referral as a first line strategy is relatively uncommon with only 11% of men and 16% of women being referred on at the first visit. However, following failure with the first line therapies, GPs are more likely to refer with over 51% of men and 58% of women being referred to a specialist or sexual health clinic.

### Sexual Health Clinics - treatment patterns

A total of 13 sexual health clinic doctors were telephoned and all completed the questionnaire. Most doctors see on average 19 cases of male genital warts and 15 cases of female genital warts per month.

Table 4 suggests that the most common first line therapy of non-cervical genital warts used by these sexual health doctors is cryotherapy for both males (63%) and females (53%), and the second most common is podophyllin in males (14%) and podophyllotoxin in females (21%).

Unlike GPs, sexual health clinic doctors use podophyllotoxin much more frequently both as a first line treatment and second line treatment in both male (12% and 17% respectively) and female patients (21% and 20% respectively). 'Other therapies' are rarely used as first line therapy (4-6%). These included trichloroacetic acid (38%), electrocautery/diathermy (32%), and combination therapy (eg. cryotherapy & podophyllin) (25%).

**Table 4:**  
**Treatment pattern for non-cervical genital warts in both men and women by sexual health doctors who responded to the survey**

<b>Males</b>	<b>First line therapy (95%CI)</b>	<b>Second line therapy (95%CI)</b>	<b>Treatment of recurrent warts (95%CI)</b>
Nil	2 (0.04-4.0)	5 (-5.6-15.6)	1 (-0.6-2.6)
Cryotherapy	63 (50.3-75.4)	44 (27.3-60.7)	68 (5.7-79.0)
Podophyllin	14 (1.5-26.5)	9 (0.8-17.2)	14 (1.3-26.7)
Podophyllotoxin	12 (0.04-24.0)	17 (3.1-30.9)	9 (1.0-17.0)
Referral	3 (-0.3-6.3)	11 (0.02-22.0)	3 (-0.3-6.3)
Other	6 (0.5-11.5)	14 (0.3-28.0)	5 (0.5-9.5)
<b>Females</b>	<b>First line therapy (95%CI)</b>	<b>Second line therapy (95%CI)</b>	<b>Treatment of recurrent warts (95%CI)</b>
Nil	2 (-0.4-4.4)	6 (-6.5-18.5)	1 (-1.0-3.0)
Cryotherapy	53 (36.9-69.1)	51 (31.4-70.6)	63 (50.3-75.7)
Podophyllin	17 (3.1-30.9)	7 (-0.4-14.4)	15 (1.7-28.3)
Podophyllotoxin	21 (4.7-37.3)	20 (2.8-37.2)	14 (1.5-26.5)
Referral	3 (0.6-5.4)	6 (0.1-11.9)	3 (0.6-5.4)
Other	4 (-0.5-8.5)	10 (-0.2-20.2)	4 (-1.3-9.3)

The most popular second line treatment for warts that failed to respond to the first line therapy for both males and females is to use cryotherapy (44% and 51% respectively) (Table 4), with podophyllotoxin being the next most common option selected. Referrals are made much less frequently representing only 11% of male second line treatment and 6% of female second line treatment.

The selected treatment option of recurrent warts in both males and females is again cryotherapy (68% and 63% respectively). This time podophyllin is second most commonly used treatment for recurrent warts in both males and females (14% and 15% respectively).

Table 5 shows the maximum number of visits per treatment to sexual health clinics by therapy type. Cryotherapy involves a maximum 3.6 visits to the clinic while podophyllin requires 0.8 of a visit less than cryotherapy. Podophyllotoxin requires up to 2 visits. There is little difference between men and women ( $p>0.05$ ).

**Table 5:**  
**Maximum number of visits required for each treatment type used in the management of external genital warts in both men and women as indicated by sexual health practitioners who responded to the survey**

Treatment type	First line therapy (95%CI)	Second line therapy (95%CI)	Treatment of recurrent warts (95%CI)
Nil	1.0 (0.4-1.6)	1.0 (0.4-1.6)	1 (0.4-1.6)
Cryotherapy	3.7 (2.9-4.5)	3.8 (2.2-5.4)	3.6 (2.7-4.5)
Podophyllin	3.0 (2.2-3.8)	2.5 (1.5-3.5)	2.9 (2.0-3.8)
Podophyllotoxin	2.3 (1.1-3.5)	1.7 (1.1-2.3)	1.8 (1.1-2.5)
Referral	1.0 (0.8-1.6)	1.2 (0.8-1.6)	1.0 (0.8-1.6)
Other	3.0 (2.2-3.8)	4.9 (1.1-8.7)	2.8 (1.9-3.7)

Referral by sexual health clinics as a first line strategy is very uncommon with only 3% of men and 3% of women being referred on at the first visit. Even as a second line treatment referral is very uncommon for both males and females (11% and 6% respectively) (Table 6). Most males are either referred to a urologist (50%) or a general surgeon (50%), while all referred female patients are referred to a Gynaecologist.

## Discussion

Although a viral aetiology was suspected for many years, the causative agent, human papillomavirus (HPV), was not confirmed until the mid-1960's. More than 60 types of HPV have now been isolated (1). Genital warts are caused by a subgroup of HPV which have a predilection for the anogenital epithelium. The entire genital tract including the vulva, vagina, cervix, penis, and urethra are susceptible to HPV infection. They are transmitted primarily through sexual contact and are only one manifestation of a broad spectrum of clinical diseases associated with HPV infection, including a strong association with genital neoplasia (1).

HPV is not easily cultured and there is there no a serologic test to detect HPV antibodies making it difficult to undertake studies designed to measure the incidence or prevalence of genital warts in the Australian community.

Experts from the Centers for Disease Control and Prevention have reviewed the literature on sexually transmitted disease treatment, systematically assessed the evidence and developed guidelines titled "*Development of sexually transmitted diseases treatment guidelines, 1993*". These guidelines include the following recommended therapies for the treatment of genital warts: cryotherapy, podophyllin, podophyllotoxin, trichloroacetic acid, electrocautery and diathermy (7). In managing a case of genital warts it is important to exclude other associated sexually transmitted diseases. The selection of treatment is highly dependent on the number, size and anatomic location of warts as well as the expense, efficacy, convenience, and potential side effects.

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The results from this survey indicate that the treatment of external genital warts is highly variable from one clinic to the next. This probably reflects the fact that no one treatment is clearly superior. To date no therapy has been shown to eradicate HPV (7). A multitude of randomised clinical trials and other treatment studies have demonstrated that currently available therapeutic methods are 22-94% effective in clearing external genital warts, and that recurrence rates are high (usually at least 25% within 3 months) with all modalities (7). Because treatment of genital warts does not eradicate HPV infection, the principle goal of therapy is the removal of warts.

The decision to conduct a survey was made on the basis that 1) we needed to produce the results quickly and there was no other recently published data regarding current treatment practices for genital warts employed by Australian general practitioners, and 2) both financial and personnel resources were limited. A survey is the simplest study to undertake, and allowed us to quickly collect planned information regarding treatment patterns of genital warts from a sample of general practitioners. However, there are a number of limitations associated with the interpretation of data collected by a survey.

First, one of the major draw backs in using any survey is the low response rate. This may be further reduced when utilising a self-completion postal questionnaire, when the response rate may be lower than that achieved by personal interviews. The postal option was selected for its speed and low cost. However, by anticipating the response rate we were able to calculate the sample size adjusting for this low level. In addition, we limited the number of questions and aimed for the questionnaire to be no longer than two pages so as to improve the response rate. Furthermore we provided reply paid addressed envelopes. We were constrained to conduct the survey over the Christmas season which may have reduced the response rate.

Second, we have assumed that the non-responders to this survey are less likely to manage cases of genital warts. The inclusion of non-responders may have led to an increase in the referral rate and a reduction in the average number of cases of genital warts managed per month. Ideally to assess the bias introduced by non-response it is essential to try and obtain some information about the individuals who initially refused to participate. However, in trying to increase the participation rate we removed any questions that would personally identify individual GPs and therefore we are unable to follow-up the non-responders.

Third, the questionnaire relied on general practitioners to recall past practices. The introduced recall bias may also significantly impact on the validity of any results. It is difficult to adjust for this in the analysis, and therefore reducing this source of bias relies on the structure and style of the questionnaire. We designed a standardised record-sheet to increase the accuracy of data recording and to facilitate data processing

A further limitation was the method of selecting our sample population. The target population is all Australian GPs. The simplest way to recruit a representative sample of GPs is to use mailing lists from the GPDs. In doing so we limited ourselves to approximately 70% of all GPs and assume that those GPs that are registered with a GPD are representative of all GPs.

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Despite these limitations we believe these data do provide valuable information from which we can determine 'typical' treatment practices of genital warts in the Australian GP community.

Results from our survey indicated that on average each GP treats approximately 0.9 cases of male genital warts and 1.1 cases of female genital warts per month. These figures are higher than those estimated by the AMTS (6) quoted above which suggest that the low response rate may have introduced a selection bias. Responders being probably more likely to treat genital warts than non-responders.

Most of the GPs treat all warts. Very few GPs (1-2%) employ no treatment and the majority (>50%) of GPs refer patients with warts resistant to initial therapy. Referral patterns were consistent with the AMTS results in which approximately 50% of female patients were referred, although a smaller proportion (20%) of male patients were referred (6).

Cryotherapy is the most common choice of first line treatment of external genital warts for both sexes. The frequency of application of cryotherapy varied from GP to GP but resulted in approximately 3 to 4 visits as the generally recommended 2-3 applications needed would require (7,8). The use of cryotherapy is highly dependent on the GP clinic actually housing the liquid nitrogen. There are overhead costs for the clinic associated with storage of liquid nitrogen: the cost of the storage container, container to dispense the nitrogen, and the ongoing costs of delivery of the nitrogen every 3 to 4 months.

As not all medical clinics store liquid nitrogen, the use of topical paint as first line treatment is the usual alternative. Approximately 30% of the GPs who responded to our questionnaire use podophyllin as first-line treatment of genital warts. Although recognised as not as effective at eliminating the warts compared to liquid nitrogen, some physicians prefer to use paint especially if the patient presents with multiple lesions. The paint (podophyllin) does not cause as much discomfort as liquid nitrogen. The application of podophyllin generally requires a weekly visit to the clinic for several weeks and in doing so requires additional GP visits as compared to cryotherapy. While podophyllin paint is relatively inexpensive, especially when only managing a handful of genital warts cases which resolve quickly, should multiple patient visits be required the cost of the visits alone make this treatment expensive.

Unlike management practices in Australian STD clinics, in the UK the topical cytotoxic therapy is the most commonly used treatment, with podophyllin being the primary treatment option selected (2).

Podophyllotoxin is a new patient-applied paint. It is surprising that only 5% of GPs prescribe this as first-line treatment. Studies comparing podophyllotoxin with podophyllin have shown podophyllotoxin is not only more effective and faster acting in the treatment of genital warts but also has fewer adverse effects over the course of the treatment (2). Podophyllotoxin can be safely used for the self-treatment of external genital warts in males and females. In Australia it is still relatively expensive for the patient with cost probably being the main inhibitory factor deterring GPs from using it. The number of GP clinic visits required are reduced significantly when

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compared to either podophyllin or cryotherapy treatments and it may be that these and savings outweigh the extra treatment costs.

Trichloroacetic acid, combination therapy, diathermy and electrocautery are other common modalities employed by GPs and STD clinics, with the more aggressive ablative therapies generally being conducted under a general anaesthetic. Other less common methods include high dose cimetidine, acyclovir and naturopathic remedies. Interferon is not an option employed by Australian GPs.

In summary, cryotherapy and topical podophyllin represent the vast bulk of first-line treatments in Australia for genital warts particularly in the General Practice sector. Podophyllotoxin certainly plays a bigger part in the treatment practices in the STD clinics particularly in the management of persistent warts. More aggressive therapies are uncommonly employed in either sectors.

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## APPENDIX

**Table 1: The response rate (%) by General Practice Division**

<b>General Practice Division</b>	<b>Response rate (%)</b>
Fairfield (NSW)	8.5
Central Coast (NSW)	18.9
Greater South East Melbourne (VIC)	26.2
Geelong (VIC)	23.5
Logan Area (QLD)	26.6
Sunshine Coast (QLD)	14.3
Adelaide Northern (SA)	14.2
Osborne (WA)	26.5