

Research paper

# Surveillance of life-long antibiotics—A cross-sectional cohort study assessing patient attitudes and understanding of long-term antibiotic consumption

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## KEYWORDS

Anti-bacterial agents;  
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**Abstract** *Background:* Some patients receive long-term or life-long antibiotics for suppression of infections deemed otherwise incurable. Little is known about the consequences of this strategy. We aimed to explore patients' attitudes towards and knowledge concerning prolonged antibiotic therapy.

*Methods:* A cross-sectional cohort pilot study of outpatients on long-term antibiotics was performed. Surveys were conducted at our healthcare network in Victoria, Australia between April and December 2015. Microbiological screening for multi-resistant organisms (MRO) was also performed.

*Results:* Heterogeneity was noted in the prescribed antibiotics and documented indications, with rifampicin and fusidic acid for suppression of prosthetic joint infection the most common regimen and indication. 41% (12/29) of participants reported side-effects attributed to their antibiotics, but 72% (21/29) still declared complete adherence to their prescribed regimen. 76% (22/29) of participants stated that they would cease their long-term antibiotics based on medical advice. 19/29 (66%) participants consented to microbiological screening and 4 were found to be colonised with MROs. They had spent more days as an inpatient in the preceding 12 months than the screened participants who were not colonised.

*Conclusion:* Participants in this study had a good understanding of their infection and the indications for their long-term antibiotic therapy, and were adherent to this therapy despite many experiencing side-effects attributed to their antibiotics. Patients who are prescribed life-long antibiotics can be carriers of multi-resistant organisms, but both the drivers of this resistance, and the broader impact of colonisation with MRO in this population is unclear.

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### Highlights

- Little is known of the possible pitfalls of long-term antibiotic use.
  - Patients on long-term antibiotics had a good understanding of their indication for prolonged therapy.
  - Despite >40% experiencing side effects attributed to prolonged antibiotic therapy, adherence was high.
  - Patients on long term antibiotics may be carriers of multi-resistant organisms.
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## Introduction

Antibiotics were first used as short-term therapy for bacterial infections. However, not long after the term antibiotic was first coined by Selman Waksman in 1941 [1], and penicillin was described as an antibacterial agent [2], the practice of using a prolonged course of antibiotics was described to treat actinomycosis [3]. Since then, the long-term or indefinite use of antibiotics has been described for a number of conditions, including suppression of prosthetic joint infections (PJI), recurrent urinary tract infection and prophylaxis in immunosuppression, post-transplantation and post-splenectomy [4–9]. Antibiotics are also sometimes prescribed for non-antibacterial effects such as immunomodulation [10,11].

We previously described the antibiotic prescribing practices at our healthcare network [12], and found that long-term antibiotic therapy represented only a small proportion of overall antibiotic prescribing (0.3% of all outpatient antimicrobial prescriptions over a 6 month period). Great heterogeneity in the prescribed antibiotic regimens was noted, and also in the documented indications for therapy. Indications included long-term suppressive therapy for infections thought incurable, such as irremovable prosthetic material, and primary and secondary prophylaxis. Additionally, many prolonged courses of antibiotics were prescribed without the involvement of infectious diseases physicians [12].

The development of antimicrobial resistance has been found to be associated with prolonged antibiotic use such as in post-splenectomy, rheumatic fever and UTI prophylaxis [9]. This is an emerging concern of global significance, at an environmental and community level [13,14]. Adverse effects associated with prolonged antibiotic consumption has also been reported [9], but little is known about pitfalls of long-term therapy experienced at an individual level.

While previous surveys have assessed patient awareness of appropriate antibiotic utilisation and issues of antimicrobial resistance [15–18], this has not been explored in the context of long-term antibiotic consumption. The aims of this study were therefore to assess patients' attitudes towards and knowledge concerning their long-term antibiotic therapy, including awareness of indication for prescription. Perceived pitfalls of prolonged therapy were also

explored, including reported adverse effects and carriage of multi-resistant organisms.

## Methods

A cross-sectional cohort pilot study was conducted of patients taking long-term antibiotics at Monash Health, a tertiary-level health service in Melbourne, Australia between April and December 2015.

Suitable participants were identified from our hospital drug management system "Merlin" (Pharmhos Software Pty. Ltd. Ver. 4.94) described in our previous study [12]. Long-term antibiotic use was defined as a course of antibacterial therapy with intent to suppress a chronic infection or to prevent recurrent infection, with a planned duration for at least 12 months. Participants were excluded if they were aged under 18 years, were unable to give informed consent, had cystic fibrosis, were prescribed antiviral therapy (e.g. for HIV or hepatitis) or antifungal therapy, or prophylaxis for in immunocompromised hosts (e.g. trimethoprim/sulfamethoxazole for Pneumocystis).

A 15 question survey was designed to be performed as a face-to-face interview (Supplementary data). Survey questions investigated several themes, including understanding of indication for long-term antibiotics, adverse effects, adherence, and attitudes towards ceasing antibiotic therapy. Surveys were conducted with face-to-face participant interviews at scheduled clinic appointments. Only patients attending the Infectious Diseases outpatient clinic at Monash Health were recruited. Participants from non-English speaking backgrounds were approached with the assistance of interpreters booked for their clinic appointments. Study investigators went through each survey question with the participant. If identified patients did not have an appointment during the study period, they were telephoned and asked if they would be interested in participating in the study. The surveys were posted to these participants along with a participant information and consent form. Information was also collected from the medical record including basic demographic data, documented antibiotic regimen and indication, previous screening for carriage of resistant organisms, and days hospitalised at our health service in the last 12 months.

Participants were asked to provide nasal and rectal swabs for screening for multi-resistant organisms, and these were collected during the clinic appointment at which consent was obtained and the survey questions answered. Nasal swabs were performed by study investigators, and rectal swabs were self-performed by the participant after careful instruction. Nasal swabs were cultured onto Brilliance methicillin resistant *Staphylococcus aureus* (MRSA)2 Agar (Thermo Fisher, Adelaide, Australia). After 24 h incubation, suspected MRSA isolates were confirmed as *S. aureus* by MALDI-TOF MS using the MALDI Biotyper system (Bruker Daltonik, Bremen, Germany). Rectal swabs were cultured directly onto a chromID VRE agar (bioMérieux, Brisbane, QLD, Australia) and CRE Chrome Agar Brilliance CRE agar (Thermo Fisher, Adelaide, Australia). After 24–48 h of incubation, any purple (*Enterococcus faecium*) or blue (*Enterococcus faecalis*) colonies were sub-cultured onto a non-selective medium [19]. Identification was confirmed as VRE by MALDI-TOF MS using the MALDI Biotyper system, and PCR testing for *dll*, *van A*, *van B* and *van C* genes were performed.

Gram-negative bacilli isolated on CRE chrome agar were identified by MALDI-TOF MS using the MALDI Biotyper system, and antimicrobial susceptibility testing using VITEK2 system. If the meropenem MIC was  $>0.25 \mu\text{g/mL}$ , isolates underwent PCR testing using primers designed for carbapenemase subgroups *blaIMP*, *blaKPC*, *blaNDM*, *blaOXA-23*-like, *blaOXA-24/40*-like, *blaOXA-48*, *blaOXA-51*-like, *blaOXA-58*-like, *blaOXA-48*-like and *blaVIM* [20].

A descriptive analysis was conducted. Statistical analyses were performed using Student's *t*-test, or Fisher Exact test where appropriate, with significance calculated at a *p*-value  $<0.05$ . Ethics approval was granted by the Monash Health Human Research and Ethics Committee. Written informed consent was obtained from all participants.

## Results

Twenty-nine participants (15 female, 14 male) completed the survey, out of 34 eligible participants identified in a previous study at our health network [12]. Two surveys were completed by participants at home and posted back, with the remaining 27 surveys performed during face-to-face interviews. Participant age ranged from 42 to 88 years (median 69) (Table 1). The indications for prolonged antibiotic therapy are recorded in Fig. 1. The most common

indication was prosthetic joint infection (16/29, 55%). Other indications included vascular graft infection, implantable cardiac device or prosthetic valve endocarditis, recurrent *S. aureus* bacteraemia, post-laminectomy infection, urinary tract infection (UTI), chronic osteomyelitis and mycotic aneurysm.

Twenty-eight of twenty-nine survey responses matched the documented indication for prolonged antibiotics recorded by their treating doctors. One participant had a response discordant to the medical record. The participant thought that they were administered life-long antibiotic therapy for suppression of UTI and chest infections, while the medical records confirmed that the indication was vascular graft infection.

The antibiotic regimens varied between participants. The most commonly prescribed antibiotics were the combination of rifampicin and fusidic acid, 9/29 (31%) participants. Other prescribed antibiotics were cefalexin (five participants), amoxicillin (4), ciprofloxacin (3), nitrofurantoin (1), clindamycin (1), penicillin (1), flucloxacillin (1), amoxicillin/clavulanic acid and pristinamycin (1), pristinamycin, trimethoprim/sulphamethoxazole and ciprofloxacin (1), rifampicin, amoxicillin and doxycycline (1).

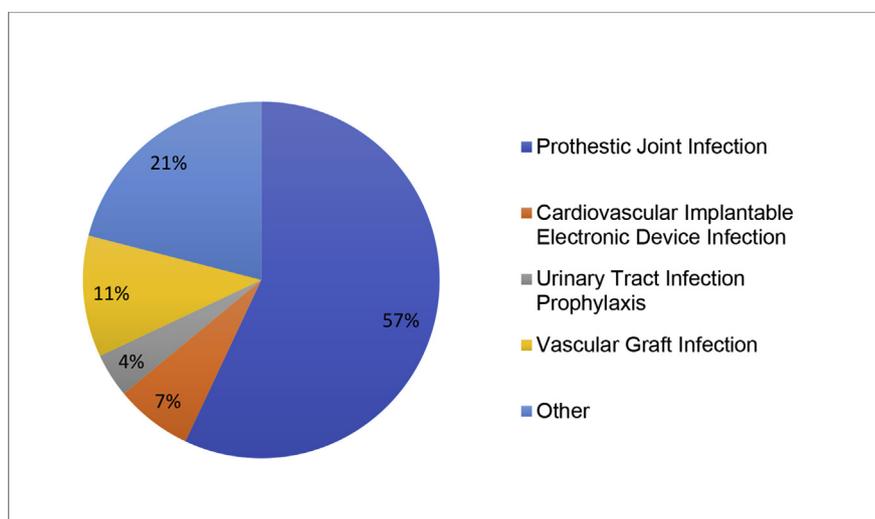
Of the 29 study participants, 19 consented to microbiological screening (Table 2, Fig. 2). The 2 participants who completed the survey on their own and posted their responses back were not screened. Six consented to collection of nasal swabs, but declined rectal swabbing. Reasons for declining microbiological screening included concerns regarding discomfort, inconvenience and time constraints of the clinic appointment having already completed the survey. Only one participant was found to be colonised with MRSA on microbiological screening, and was notably on life-long cefalexin for recurrent methicillin susceptible *S. aureus* (MSSA) bacteraemia. This participant also isolated VRE on their rectal screening swab. Two participants were noted to have previously isolated MRSA from clinical specimens (wound swabs, bloods cultures), however MRSA was not isolated on screening swabs performed at the time of the study.

VRE was detected on rectal swabs in three participants. All of the VRE isolates were *Enterococcus faecium*, expressing the *VanB* gene. Two participants were on long-term amoxicillin/clavulanic acid and ciprofloxacin, and another on long-term flucloxacillin and ciprofloxacin for chronic bone/joint infection. Four other participants had previously screened positive for VRE, and repeat screening

**Table 1** Participant demographics.

|   | Total cohort | Screened and colonised with MROs | Screened and not colonised with MROs | Significance                                      |
|---|--------------|----------------------------------|--------------------------------------|---|
| Sample size                               | 29           | 4                                | 15                                   |   |
| Age (median years)                        | 69           | 76.5                             | 70                                   |   |
| Age (mean years)                          | 68           | 76.8                             | 68.8                                 |   |
| Sex male/%                                | 14 (48)      | 2 (50)                           | 6 (40)                               |   |
| Years taking antibiotics (mean)           | 3.2          | 2                                | 3.6                                  |   |
| Days in hospital in last 12 months (mean) | 12.5         | 21.8                             | 8.5                                  | <i>t</i> -value = 1.72,<br><i>p</i> -value = 0.05 |

MRO, Multi-resistant organisms.



**Figure 1** Documented indications for prolonged antibiotic therapy.

was not performed on these participants in accordance with local laboratory policy.

One participant had positive microbiological swabs for a carbapenem-resistant *Enterobacter cloacae*, however it did not produce a carbapenemase. This participant was prescribed long-term amoxicillin/clavulanic acid and pristinamycin for suppression of a VRE vascular graft infection. Of the five participants colonised with resistant organisms, three had been commenced on long-term antibiotic therapy greater than 12 months prior to the study.

Participants who were found to be colonised with resistant organisms spent a median of 20.5 days (mean 21.8 days) in hospital in the 12 months prior to the study, compared to the median stay of 0 (mean 8.47 days) in the 15 participants who were screened but tested negative for resistant organisms ( $t$ -value = 1.72,  $p$ -value = 0.05) (Table 1).

Twelve (41%) participants reported adverse effects associated with the antibiotics they were prescribed. These included nausea/vomiting, diarrhoea, weight gain, stomach discomfort, reflux, thrush and drug–drug interactions (Fig. 3). Eight participants stated these were experienced every day. Of the remaining four, one stated they experiencing these weekly, one had symptoms monthly, one reported symptoms yearly, and one reported side-effects if tablets were taken before meals. Sixteen participants (55%) recalled being told by their doctor that they may experience side-effects related to their medication before commencing antibiotics, however ten stated they were not made aware of potential side-effects, and two were unsure whether a discussion had taken place. There was no difference in rates of reported adverse effects in participants found to be colonized with MROs compared to those not colonized (2/4 vs 3/15  $p$  value 0.27).

Reported adherence to therapy was high, with 21 (72%) participants reporting never missing any tablets. Of the seven participants who reported missing tablets, four forgot, two stated they were on too many tablets and one missed for an unknown reason. One participant did not answer the question. Those who reported missing doses stated that they missed between 1 and 6 tablets over a one-

month period. Those who reported side effects were not more willing to cease treatment (2/12 vs 4/12  $p$  = 0.16).

Participants were asked if they would seek medication advice if they acquired another infection while on life-long antibiotic therapy. Twelve stated they were more likely to seek medical advice in such a situation and none said that they would be less likely to obtain advice. 21/29 (72%) stated that they would not consider ceasing antibiotics if there was a chance of relapse of their initial infection. Six participants would consider antibiotic therapy, and one was unsure. Furthermore, when asked at what point participants would consider stopping their antibiotic usage, 22/29 (76%) stated that they would consider ceasing antibiotics based on medical advice, while one would consider stopping treatment in five years. One participant would never consider ceasing therapy and five participants did not respond to the question.

## Discussion

We conducted a survey of outpatients prescribed long-term antibiotics through our health network to assess understanding and acceptability of prolonged antibiotic consumption, as well as perceived pitfalls to this type of therapy. Microbiological screening for MROs was also conducted at the time in consenting participants. Our small survey sample demonstrates heterogeneity in indications for prolonged antibiotic therapy at our health network as well as a wide range of antibiotic regimens used in long-term therapy. Our participants generally have a good understanding of their infection and indication for life-long therapy, with all but one respondent stating an indication for antibiotics that matched their medical records. All of the participants reported that they were just as likely, or more likely to seek medical advice if they thought they had acquired another infection, indicating that they would not assume that their current antibiotic regimen would protect them from other infections.

The majority of our participants on life-long antibiotics were taking therapy for PJI. A predominance of rifampicin

**Table 2** Summary of participants who consented to microbiological screening.

| Age (yrs)                        | Gender | Antimicrobial/s prescribed                         | Indication <sup>a</sup>                          | Days admitted to hospital in previous 12 months | AEs reported                                     |
|----------------------------------|--------|--|--|---|--|
| <b>MRO not isolated (n = 15)</b> |        |  |  |   |  |
| 65                               | M      | Cefalexin  | Recurrent MSSA bacteraemia for prostatic abscess | 1   | No   |
| 70                               | M      | Amoxycillin  | Prosthetic valve endocarditis                    | 20  | Nausea/vomiting                                  |
| 76                               | F      | Rifampicin, Fusidic acid                           | MRSA chronic hip osteomyelitis                   | 0   | No   |
| 69                               | F      | Rifampicin, Fusidic acid                           | Prosthetic joint infection                       | 0   | Nausea/vomiting<br>Diarrhoea<br>Rash/itch        |
| 73                               | F      | Amoxycillin  | Prosthetic metalware from laminectomy infection  | 0   | No   |
| 70                               | M      | Cefalexin  | Recurrent MSSA bacteraemia                       | 32  | Other  |
| 42                               | F      | Nitrofurantoin                                     | UTI prophylaxis                                  | 21  | Other  |
| 68                               | M      | Pristinamycin, fluconazole, TMP/SMX, ciprofloxacin | Vascular graft infection                         | 0   | Nausea/vomiting                                  |
| 86                               | F      | Rifampicin, Fusidic acid                           | Prosthetic joint infection                       | 0   | No   |
| 78                               | M      | Rifampicin, Fusidic acid                           | Prosthetic joint infection                       | 0   | No   |
| 87                               | F      | Rifampicin, Fusidic acid, Ciprofloxacin            | Prosthetic joint infection                       | 29  | No   |
| 71                               | F      | Ciprofloxacin                                      | Prosthetic metalware from laminectomy infection  | 0   | No   |
| 63                               | F      | Rifampicin, Amoxycillin, Doxycycline               | Prosthetic joint infection                       | 0   | No   |
| 45                               | F      | Rifampicin, Fusidic acid                           | Prosthetic joint infection                       | 6   | No   |
| 69                               | F      | Ciprofloxacin                                      | Prosthetic joint infection                       | 18  | No   |
| <b>MRO isolated (n = 4)</b>      |        |  |  |   |  |
| 66                               | F      | Ciprofloxacin, Flucloxacillin                      | Prosthetic joint infection                       | 31  | Nausea/vomiting<br>Diarrhoea<br>Rash/itch<br>DDI |
| 79                               | M      | Amoxicillin/clavulanic acid, Ciprofloxacin         | Prosthetic joint infection                       | 1   |  |
| 74                               | M      | Amoxicillin/clavulanic acid, Pristinamycin         | Vascular graft infection                         | 10  |  |
| 88                               | F      | Cefalexin  | Recurrent MSSA bacteraemia                       | 45  |  |

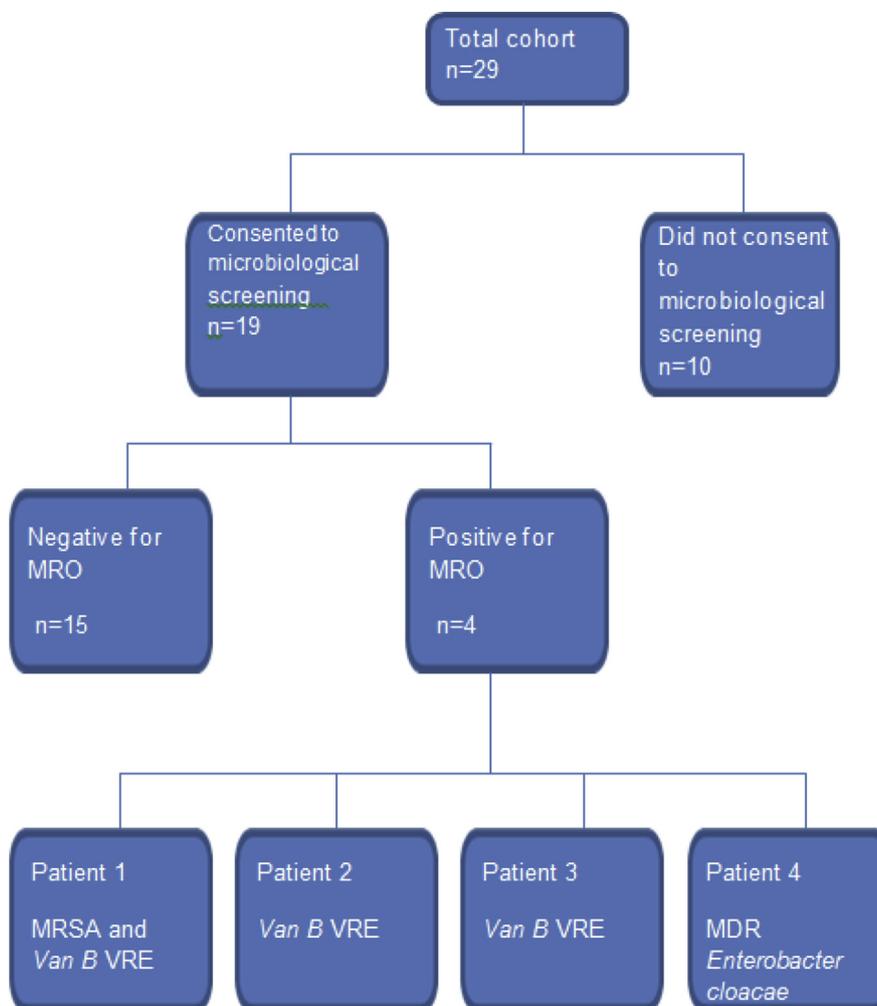
M, male; F, female; MSSA, Methicillin susceptible *Staphylococcus aureus*; MRO, multi-resistant organism; DDI, drug–drug interactions; AE, adverse; n, number.

<sup>a</sup> Indication for life-long antibiotics.

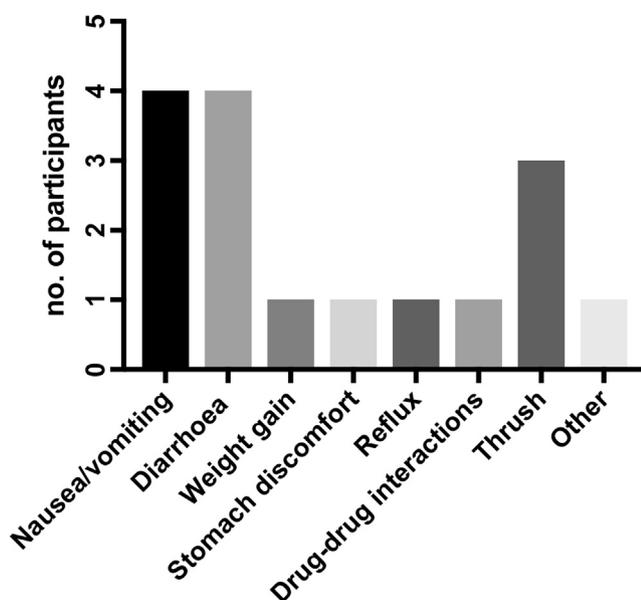
and fusidic acid therapy was noted, in contrast with only one participant prescribed flucloxacillin. MSSA is isolated in more frequently in PJI at our health network, and this is mirrored in published local data [21]. Antibiotics for treatment of MSSA infections (eg cefalexin, flucloxacillin) are able to be prescribed by primary care clinicians and dispensed by community pharmacies. However, rifampicin, which is not subsidised for MRSA infection by the Australian Pharmaceutical Benefits System (PBS), is usually dispensed by hospital pharmacies, which may explain the over-representation of MRSA and rifampicin and fusidic acid combinations in our data. Despite a recent study demonstrating drug–drug interactions between fusidic acid and rifampicin, causing lowered fusidic acid levels [22], rifampicin and fusidic acid combination therapy is accepted and

utilised in Australia for both acute PJI and suppressive therapy, with relative success [23].

Almost half of the surveyed participants reported adverse effects attributed to taking prescribed prolonged antibiotics, which were mainly gastrointestinal in nature. However, experiencing adverse effects this did not appear to impact on reported adherence to therapy. This may reflect an understanding or anxiety from patients around the risks of relapsed infection if suppression is stopped. This may also mirror the attitudes of prescribing physicians who counselled these patients upon commencing these antibiotics. This highlights the importance of ongoing discussion between the clinician and patient regarding adverse effects of long-term therapy, particularly when it results in decreased adherence. Clinicians should address



**Figure 2** Participants who were screened for multi-resistant organisms. MRO, Multi-resistant organism; MRSA, Methicillin resistant *Staphylococcus aureus*; VRE, Vancomycin resistant enterococcus.



**Figure 3** Side effects reported by participants.

and assist in minimising antimicrobial side effects where possible.

Over 20% of the participants who underwent MRO screening were found to be colonised with resistant organisms. *VanB* VRE was the most common resistant organism identified in this cohort. Of note, all of the carriers of VRE were prescribed long-term ciprofloxacin (in combination with amoxicillin/clavulanic acid or flucloxacillin), and the participant colonised with a carbapenem-resistant organism was also prescribed combination therapy including ciprofloxacin. MRSA was detected on nasal swab for 5% of participants which is a higher incidence than reported elsewhere (an Australian study reported a colonisation rate of 1.7% from nasal swabs [24]). VRE was detected on rectal swab for 16% participants, which is consistent with an Australian point prevalence study which reported an inpatient prevalence of 17.5% [25]. These studies were performed on inpatients, while our population were outpatients, and our small sample size may have overestimated prevalence.

It is unclear what impact duration of long-term antibiotics had on whether a participant was colonised with

resistant organisms. Over half of the participants colonised with multi-resistant organisms had been commenced on long-term antibiotic therapy greater than 12 months prior. The number of days as an inpatient in the 12 months leading up to the study also appeared to be important, with the colonised participants having an average length of stay greater than twice that of the non-colonised ones. Our small study was unable to ascertain whether admission to hospital in the previous 12 months was related, either as a cause or effect, to colonization with MROs.

This study has several limitations. The population of patients on life-long antibiotic therapy for suppression of infections thought incurable at our health network is small [12], and therefore only 29 participants were recruited in the study time period. Only medical records from our healthcare network were reviewed, and data from other hospitals or primary care was not analysed. Additionally, only outpatients to Infectious Diseases clinic at our health network were surveyed and screened, so outpatients seen by other units such as respiratory or general medicine were not included in our study. This restricted sample size and the ability to collect prescribing data, thus we were unable to comment on the impact of confounders such as comorbidities on MRO colonisation and length of stay. Nasal sampling alone for MRSA has a lower sensitivity than sampling of nasal and other sites [24], so we may have underestimated the true carriage rate of MRSA in our population. Our sample is also biased in that it selects by design those who elect to stay in care and continue to attend in order to receive ongoing antimicrobial prescriptions. Conducting surveys with interviewers also leads to the potential for observer and recall bias, which could impact accurate reporting on participants' true attitudes and views.

Our study was exploratory but looked at a group of patients who may be important in the ecology of hospital antimicrobial resistance: patients prescribed long-term antibiotics who may be frequent health service consumers. We found that a proportion of participants were colonised with MROs, though the drivers of resistance in these individuals are unclear. This study demonstrates that there is scope to further explore these questions on a larger scale, through a multi-site prospective cohort study including patients from all medical and surgical units. This work should explore the actual benefits of long-term suppressive therapy in infection, including the rate of actual suppression of infection, as well as significant challenges to this therapy, such as long-term adherence rates and side-effects, and any effects on the microbiome of the individuals involved. Finally, our study highlights the importance of robust local antimicrobial guidelines and antimicrobial stewardship programs in ensuring that when antimicrobials are prescribed, that they are at an appropriate dose and duration for the indication.

This study shows that patients who are prescribed life-long antibiotic therapy can be carriers of multi-resistant organisms, that these patients tend to be on broad-spectrum combination antibiotic therapy, and have recently spent more time as an inpatient than their non-colonised counterparts. It is not known to what extent this colonisation has on the burden of antibiotic resistance in hospitals.

We found that patients on prolonged courses of therapy have a good understanding of their infection and the indications for their long-term therapy. While many experienced side-effects attributed to their antibiotics, many patients were aware of the potential for these when they commenced treatment, and this does not appear to have an effect on adherence.

More research is needed to explore the link between long-term antibiotic use, and the effect on the microbiome. In particular, the risk of colonisation with multi-resistant organisms, and whether colonisation translates to deleterious clinical outcomes. With over three quarters of our surveyed participants indicating they would consider ceasing their life-long therapy if advised to by their medical practitioner, there is scope for designing a study to determine if long-term antibiotics can be safely ceased in a carefully selected cohort of patients.

## Ethics

Ethics approval was granted by the Monash Health Human Research and Ethics Committee (14379A), and written informed consent was obtained from all participants.

## Authorship statement

JL and IW designed the participant surveys. JL, MB, IW and TK collected informed consent and survey responses, and performed nasal swabs on consenting participants. JL, SB and RS collated and analysed the data. JL and IW interpreted the data and determined the conclusions of the study. All authors read and approved the final manuscript.

## Conflicts of interest

The authors declare that they have no competing interests.

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## Provenance and peer review

Not commissioned; externally peer reviewed.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.idh.2019.05.002>.

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