

# Clinical and Ecological Impact of an Educational Program to Optimize Antibiotic Treatments in Nursing Homes (PROA-SENIOR): A Cluster, Randomized, Controlled Trial and Interrupted Time-Series Analysis

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**Background.** Antimicrobial stewardship programs (ASPs) are recommended in nursing homes (NHs), although data are limited. We aimed to determine the clinical and ecological impact of an ASP for NHs.

**Methods.** We performed a cluster, randomized, controlled trial and a before–after study with interrupted time-series analyses in 14 NHs for 30 consecutive months from July 2018 to December 2020 in Andalusia, Spain. Seven facilities implemented an ASP with a bundle of 5 educational measures (general ASP) and 7 added 1-to-1 educational interviews (experimental ASP). The primary outcome was the overall use of antimicrobials, calculated monthly as defined daily doses (DDD) per 1000 resident days (DRD).

**Results.** The total mean antimicrobial consumption decreased by 31.2% (−16.72 DRD;  $P = .045$ ) with respect to the preintervention period; the overall use of quinolones and amoxicillin–clavulanic acid dropped by 52.2% ( $P = .001$ ) and 42.5% ( $P = .006$ ), respectively; and the overall prevalence of multidrug-resistant organisms (MDROs) decreased from 24.7% to 17.4% ( $P = .012$ ). During the intervention period, 12.5 educational interviews per doctor were performed in the experimental ASP group; no differences were found in the total mean antimicrobial use between groups (−14.62 DRD;  $P = .25$ ). Two unexpected coronavirus disease 2019 waves affected the centers increasing the overall mean use of antimicrobials by 40% (51.56 DRD;  $P < .0001$ ).

**Conclusions.** This study suggests that an ASP for NHs appears to be associated with a decrease in total consumption of antimicrobials and prevalence of MDROs. This trial did not find benefits associated with educational interviews, probably due to the coronavirus disease 2019 pandemic.

**Clinical Trials Registration.** NCT03543605.

**Keywords.** antimicrobial stewardship; nursing home; long-term care facility; antibiotic prescribing; antimicrobial resistance.

Received 22 July 2022; editorial decision 13 October 2022; published online 21 October 2022

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**Clinical Infectious Diseases**® 2023;76(5):824–32

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<https://doi.org/10.1093/cid/ciac834>

There are more than 63 000 nursing homes (NHs) in Europe with approximately 3.6 million residents, and the number is increasing [1, 2]. In these facilities, the frequent use of devices for medical procedures and the common areas shared by caregivers facilitate the acquisition and dissemination of multidrug-resistant organisms (MDROs). The overuse and misuse of antibiotics are known as important risk factors of antimicrobial resistance (AMR) and also increase the risk of side effects and drug interactions in NH residents [3–5].

Antimicrobial stewardship programs (ASPs) are recommended interventions to improve antimicrobial use and combat the growing threat of AMR [3, 6, 7]. Their clinical and ecological benefits have been demonstrated in hospitals as

well as in the community [8–12], but evidence of the effectiveness of these programs in NHs is limited [13–15].

We conducted a cluster, randomized, clinical trial (cRCT) and before–after study with interrupted time-series analysis (ITSA) aimed to assess the effect of an education-based ASP specifically designed for NHs on the use of antimicrobials and clinical and ecological outcomes and to determine whether supplementing the ASP with 1-to-1 educational interventions would achieve superior outcomes.

## METHODS

### Study Design

PROA-SENIOR was a parallel-group cRCT with a before–after study and ITSA conducted from 1 July 2018 to 31 December 2020 in the 14 existing public NHs with a capacity of 1667 resident beds and 27 physicians in Andalusia, Spain. The preintervention phase started on 1 July 2018 and lasted 8 months.

The participating facilities were stratified before randomization based on facility size and percentage of residents with dependency and randomized (1:1). One group implemented an ASP with general educational intervention measures (general ASP), and the other (experimental ASP) implemented the same general ASP plus educational interviews. As the implementation of ASPs is a recommended practice by international organizations [3], a control group without intervention was not included.

This study followed the Consolidated Standards of Reporting Trials guideline and was approved by the University Hospitals Virgen Macarena and Virgen del Rocío Ethics Committee. Written informed consent was obtained from all patients who participated in the microbiological sampling or their legally authorized representatives. Clinical staff and facility participants were masked to study group allocation during recruitment and preintervention assessment but not for the intervention. The statistical analysis was not blinded. Patient data were anonymized.

### Intervention

The general ASP intervention consisted of implementation of a bundle of the following educational measures: creation of a local ASP team at each NH composed of the center’s physicians, nurses, and pharmacist; presentation of the intervention by the local teams at their own centers; selection of a specific guideline as a reference document for the diagnosis and treatment of infectious diseases in NHs [16]; delivery of educational support material on the rationale, objectives, and methodology of the trial and recommendations for the clinical management of the main clinical syndromes in residents (Supplementary Table 1); and feedback of results through quarterly reports and meetings, nominal and disaggregated by centers, to all participating teams.

The intervention of the experimental ASP consisted of implementation of the measures described in the general ASP plus educational interviews, that is, a 1-to-1 peer training activity aimed primarily at modifying prescribing behaviors when they are inappropriate and reinforcing them when they are correct [9, 11]. The interviews were carried out via telephone by 1 of the researchers, a specialist in infectious diseases (J. M. C.), with each of the doctors at the experimental ASP NHs following a structured questionnaire (Supplementary Figure 1). Prescriptions were rated as appropriate when all questions were assessed positively. At the end of the interview, the NH doctor was invited to complete an anonymous satisfaction survey on the usefulness of the activity (Supplementary Figure 2). The procedure is detailed in Supplementary Methods S1.

### Outcomes

The primary outcome was the overall use of antimicrobials for systemic use (Anatomical Therapeutic Chemical codes J01 + J02), calculated monthly as defined daily doses (DDD) per 1000 resident days (DRD), according to the World Health Organization’s ATC/DDD alterations informed in 2019 [17].

Secondary outcomes were the antimicrobial prescribing profile, measured as the DRD of amoxicillin–clavulanic acid, quinolones, fosfomycin trometamol, amoxicillin, cephalosporins, cloxacillin, clarithromycin, azithromycin, cotrimoxazole, and other antimicrobials; prevalence of MDRO colonization, measured in a sample of residents, assessed by the presence in rectal swabs of extended-spectrum  $\beta$ -lactamase–producing (ESBL) Enterobacterales, carbapenemase–producing Enterobacterales, MDR *Pseudomonas aeruginosa* and MDR *Acinetobacter baumannii*, and methicillin-resistant *Staphylococcus aureus* (MRSA) in nasal smears (microbiological procedures are detailed in Supplementary Methods S2); severe adverse effects of antimicrobials, measured by incidence density, defined as the number of hospital admissions due to adverse effects of antimicrobials per 1000 resident days; hospital admissions due to infections, measured by incidence density, defined as the number of hospital admissions per 1000 resident days; and assessment of the educational interviews by the physicians, measured as the number of satisfaction surveys with positive responses divided by the total number of responded surveys.

### Statistical Analyses

We did an exhaustive sampling that included the 14 existing public NHs. For the cRCT analysis, we performed a linear mixed-effects model (LMM) regression for repeated measures with random intercepts to evaluate the effect of the ASP on antimicrobial use, MDRO prevalence, and incidence density outcomes in all NHs and to compare the differences in the estimated marginal means of the variables under study between

the 2 arms [18, 19]. We also carried out a before–after analysis to examine the changes in trend and level associated with the intervention in the 30-month series and estimated the intergroup differences in trends using an ITSA [20, 21].

Intergroup comparisons of the baseline characteristics of the NHs and MDRO prevalence were evaluated using  $\chi^2$  tests for categorical data and Student *t* or Mann–Whitney *U* tests for continuous data. The Pearson correlation was used to evaluate associations between antimicrobial use and the prevalence of MDRO. Analyses were done with IBM SPSS Statistics (version 23.0) and R (version 4.0.5), considering a *P* < .05 (2-tailed) as significant. Statistical procedures are detailed in [Supplementary Methods S3](#).

## RESULTS

### Recruitment and Follow-up

The study was conducted for 30 months at the 14 public NHs in Andalusia, Spain. The preintervention phase started on 1 July 2018 and lasted 8 months. There were no significant differences in the baseline characteristics between the 2 randomized groups in the preintervention phase ([Table 1](#)). Between 1 March 2019 and 30 June 2019 (the phase-in period), baseline results for antimicrobial use as well as the scheduled interventions were presented to the participating NHs. The intervention period started on 1 July 2019 simultaneously at all the centers, with 7 randomly assigned to the general ASP group and 7 to the experimental ASP group ([Figure 1](#)), and lasted 18 months until 31 December 2020. The average monthly number of residents during the study period was  $1501 \pm 65$  ([Supplementary Table 2](#)).

All NH doctors participated in the study, 12 in the general ASP group and 14 in the experimental ASP group; 1 doctor passed away due to coronavirus disease 2019 (COVID-19) in April 2020. MDRO infection prevention and control measures remained unchanged throughout the prepandemic phase of the study.

### Antibiotic Use

The ASP reduced the all-center mean total antimicrobial use by 31.2% (–16.72 DRD; *P* = .045) with respect to preintervention values, in particular, for amoxicillin–clavulanic acid and quinolones. Overall mean use of both antibiotics dropped by 42.5% (–5.77 DRD; *P* = .006) and 52.2% (–7.76 DRD; *P* = .001), respectively ([Table 2](#)). There was no change in mean consumption between periods for all other antibiotics listed, except for a reduction in cloxacillin ([Supplementary Table 3](#)). No significant differences in mean antimicrobial consumption were found between groups during the intervention, except for azithromycin use, which was 73.1% lower in the experimental ASP group (intergroup difference = –5.11 DRD; *P* = .027; [Table 2](#), [Supplementary Table 3](#)). The quarterly evolution of the

prescription of the different classes of antibiotics throughout the study is shown in [Supplementary Figure 3](#).

The ITSA confirmed and provided further information on all of these findings. All-center total antimicrobial consumption decreased promptly after the start of the intervention (–35.37 DRD; 95% confidence interval [CI], CI –59.18 to –11.56), reversing the preintervention increasing trend (2.77 DRD per month; 95% CI, .01 to 5.54) to a stable trend throughout the intervention period (change in trend = –2.73; 95% CI, –5.33 to –.13). Significant prompt reductions and changes toward decreasing trends after the inception of the ASP were found in the use of quinolones, amoxicillin–clavulanic acid, cephalosporins, and azithromycin, with both study groups behaving similarly ([Figure 2](#), [Supplementary Table 4](#)). No statistical differences were found between groups in the trend slopes during the intervention period, except for azithromycin (*P* = .0007) and cotrimoxazole (*P* = .006; [Supplementary Table 5](#), [Supplementary Figures 4–6](#)).

The COVID-19 pandemic impacted NHs during the last year of the intervention period ([Supplementary Table 6](#)). The mixed-effects analysis identified significant increases in the overall mean use of total antimicrobials of 40% (51.56 DRD; 95% CI, 37.20 to 65.92), 6% for amoxicillin–clavulanic acid (8.27 DRD; 95% CI, 4.65 to 11.90), 20% for quinolones (8.55 DRD; 95% CI, 4.62 to 12.48), 249% for cephalosporins (20.81 DRD; 95% CI, 13.25 to 28.37), and 319% for azithromycin (14.22; 95% CI, 9.27 to 19.18) in the months when the COVID-19 epidemic struck the participating facilities, with respect to the mean use in the intervention period. These increases were smaller in the experimental ASP group than in the general ASP group NHs (–78.20; 95% CI, –110.58 to –45.82; [Supplementary Table 7](#)).

### MDRO Prevalence

Rectal and nasal swabs were collected in June 2019 from 462 (30%) residents who were resampled in the fourth quarter of 2020, except for 77 individuals who either died or left the NHs during the intervention period.

Overall, the most prevalent bacteria at baseline were MDR gram-negative bacilli (16.2%), represented mainly by ESBL *Escherichia coli* (14.3%), and MRSA (8.5%). Initially, 1 in 4 NH residents was colonized by an MDRO (24.7%); 1.5 years after implementation of the ASP, that ratio decreased to 1 in 6 (17.4%), a significant reduction of 7.3% age points (*P* = .012). This decrease was mainly driven by the decrease in MDR gram-negative bacilli, especially ESBL *E. coli*. No intergroup significant differences were found at the end line ([Table 3](#)).

For the entire study period, we found a positive correlation between total DRD of antimicrobial consumption and MDRO prevalence (*r* = 0.52; *P* = .005) as well as between the use of quinolones and ESBL *E. coli* (*r* = 0.45; *P* = .017).

**Table 1. Baseline Characteristics of Nursing Homes**

Characteristic	Total	General ASP Group	Experimental ASP Group	P Value
Nursing homes, no.	14 (100%)	7 (50%)	7 (50%)	.99
Facility size, no. of beds	110 (86–140)	114 (70–157)	110 (91–134)	.90
Occupancy, no. of residents	99 (82–123)	100 (65–136)	99 (85–115)	.90
Dependent residents, %				
<85	7 (50)	4 (57)	3 (43)	.59
≥85	7 (50)	3 (43)	4 (57)	.59
No. of doctors	2.0 (1–4)	2.0 (1–3)	2.0 (1–4)	.62
Total antimicrobial use, DRD	49.04 (26.00–79.43)	45.93 (27.82–81.72)	52.15 (26.23–56.96)	.95
Amoxicillin–clavulanate, DRD	12.92 (7.87–16.24)	8.81 (7.10–14.43)	16.14 (4.95–24.86)	.26
Quinolones, DRD	9.80 (6.64–25.12)	9.36 (8.01–27.14)	10.23 (6.57–14.14)	.38
Fosfomycin–trometamol, DRD	1.05 (0.30–2.06)	1.40 (1.03–3.04)	0.30 (0.21–1.56)	.17
Amoxicillin, DRD	1.87 (1.19–2.50)	2.09 (0.99–2.62)	1.85 (1.48–1.93)	.95
Cephalosporins, DRD	6.36 (3.17–9.89)	9.02 (3.64–16.14)	4.42 (3.58–8.07)	.32
Cloxacillin, DRD	0.22 (0.03–1.15)	0.19 (0.05–0.43)	1.15 (0.06–1.97)	.28
Clarithromycin, DRD	0.14 (0.00–0.74)	0.00 (0.00–1.49)	0.27 (0.00–0.67)	.95
Azithromycin, DRD	4.96 (1.07–10.01)	6.70 (4.96–9.58)	1.97 (0.95–6.24)	.38
Cotrimoxazole, DRD	0.49 (0.00–1.49)	0.69 (0.14–1.22)	0.00 (0.00–2.61)	.95
Other antimicrobials, DRD	1.14 (0.58–2.30)	0.70 (0.48–1.30)	1.31 (0.82–3.72)	.32
Prevalence of resistant bacteria, <sup>a</sup> (%)	114/462 (24.7)	73/282 (25.9)	41/180 (22.8)	.51
Hospital admissions due to infections, <sup>b</sup> incidence density	0.255 (0.210–0.320)	0.260 (0.200–0.365)	0.250 (0.225–0.300)	.71

Data are n (%) or median (interquartile range).

Abbreviations: ASP, antimicrobial stewardship program; DRD, defined daily doses per 1000 resident days.

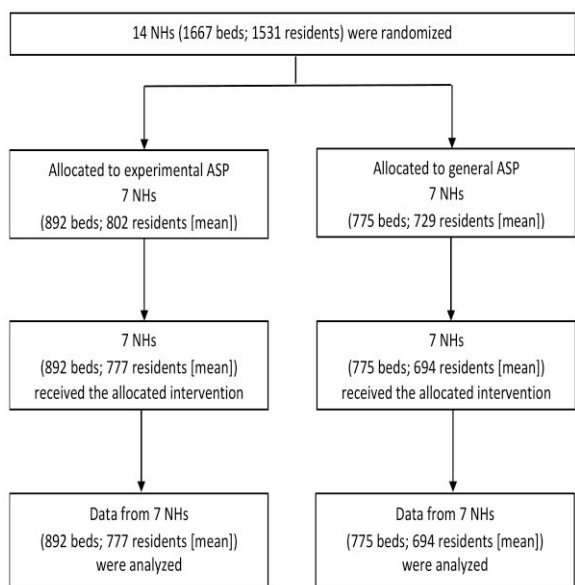
<sup>a</sup>Percentage of isolates of quinolone-resistant *Escherichia coli*, or extended-spectrum β-lactamase-producing *E. coli*, or carbapenemase-producing Enterobacterales, or methicillin-resistant *Staphylococcus aureus*.

<sup>b</sup>Number of residents admitted to a hospital due to an infectious disease per 1000 resident days.

### Clinical Outcomes

Hospital admissions due to infections remained stable during the study, showing no differences between periods (0.038 admissions per 1000 resident days;  $P = .67$ ) and intervention

groups ( $-0.020$ ;  $P = .84$ ). There was also no difference in the hospital admissions for adverse effects of antimicrobials when the 2 periods were compared ( $-0.013$  admissions per 1000 resident days;  $P = .66$ ) and for the 2 intervention groups ( $0.007$ ;  $P = .36$ ; [Supplementary Table 8](#)).



**Figure 1.** Trial profile. Abbreviations: ASP, antimicrobial stewardship program; NH, nursing home.

### Educational Interviews and Appropriate Prescribing

A total of 163 educational interviews were conducted in the experimental ASP group NHs, resulting in 12.5 per doctor. During the pandemic, the number of interviews was significantly reduced compared with the prepandemic period (3.9 vs 15.5 average interviews per month;  $P = .004$ ; [Supplementary Figure 7](#)). A total of 152 (93%) educational interviews were conducted on clinical cases with empirical antimicrobial treatments; the remainder were conducted on clinical cases with targeted treatments. The distribution of educational interviews by syndromes was as follows: respiratory tract infections (RTIs; 37%;  $n = 60$ ), followed by urinary tract infections (UTIs; 30%;  $n = 49$ ), skin and soft tissue infections (21%;  $n = 34$ ), other infections (9%;  $n = 15$ ), and prophylaxis (3%;  $n = 5$ ). A total of 47.2% (77 of 163) of the treatments reviewed were rated as inappropriate. The main cause of inappropriateness was excessive treatment duration (26%), followed by the incorrect antimicrobial selection (20%; [Supplementary Table 9](#)). Eight of 13 (62%) doctors responded to the satisfaction survey; all of them rated the intervention as useful.

**Table 2. Effect of the Intervention on the Use of Total Antimicrobials, Amoxicillin–Clavulanic Acid, Quinolones, and Fosfomycin Trometamol**

Nursing Homes Group	Baseline Period July 2018–February 2019, Mean (95% CI)	Intervention Period July 2019–December 2020, Mean (95% CI)	Mean Difference <sup>a</sup> (95% CI)	P Value <sup>a</sup>	Intergroup Mean Difference <sup>b</sup> (95% CI)	P Value <sup>b</sup>
<b>Total antimicrobials</b>						
All NHs	53.52 (33.89 to 73.14)	36.79 (23.45 to 50.14)	–16.72 (–27.04 to –9.66)	.045	...	
Experimental ASP group	50.78 (34.09 to 67.47)	29.36 (16.54 to 42.17)	–21.42 (–34.99 to –7.87)	.002	–14.62 (–40.76 to 11.52)	.25
General ASP group	56.40 (22.01 to 90.79)	43.98 (17.71 to 70.26)	–12.42 (–40.28 to 15.44)	.38		
<b>Amoxicillin–clavulanic acid</b>						
All NHs	13.59 (9.30 to 17.87)	7.82 (5.71 to 9.92)	–5.77 (–9.91 to –1.63)	.006	...	
Experimental ASP group	17.16 (10.87 to 23.46)	7.65 (4.06 to 11.24)	–9.51 (–15.57 to –3.46)	.002	–0.19 (–4.60 to 4.22)	.93
General ASP group	10.55 (4.60 to 16.49)	7.84 (4.53 to 11.16)	–2.71 (–8.36 to 2.95)	.35		
<b>Quinolones</b>						
All NHs	14.87 (9.58 to 20.15)	7.11 (3.63 to 10.58)	–7.76 (–12.22 to –3.30)	.001	...	
Experimental ASP group	11.46 (6.92 to 16.01)	4.35 (2.22 to 6.48)	–7.11 (–11.57 to –2.66)	.002	–5.48 (–12.24 to 1.28)	.10
General ASP group	18.16 (9.23 to 27.10)	9.83 (3.20 to 16.46)	–8.33 (–15.74 to –.93)	.028		
<b>Fosfomycin trometamol</b>						
All NHs	1.68 (.10 to 3.27)	2.35 (1.21 to 3.49)	0.67 (–.58 to 1.91)	.29	...	
Experimental ASP group	.89 (–.38 to 2.16)	1.59 (.63 to 2.56)	0.70 (–.31 to 1.71)	.17	–1.51 (–3.70 to 0.68)	.16
General ASP group	2.44 (–.45 to 5.33)	3.10 (.86 to 5.35)	0.66 (–1.62 to 2.94)	.57		

Data are expressed in defined daily doses per 1000 resident-days.

Abbreviations: ASP, antimicrobial stewardship program; CI, confidence interval; NH, nursing home.

<sup>a</sup>Mean difference between periods.

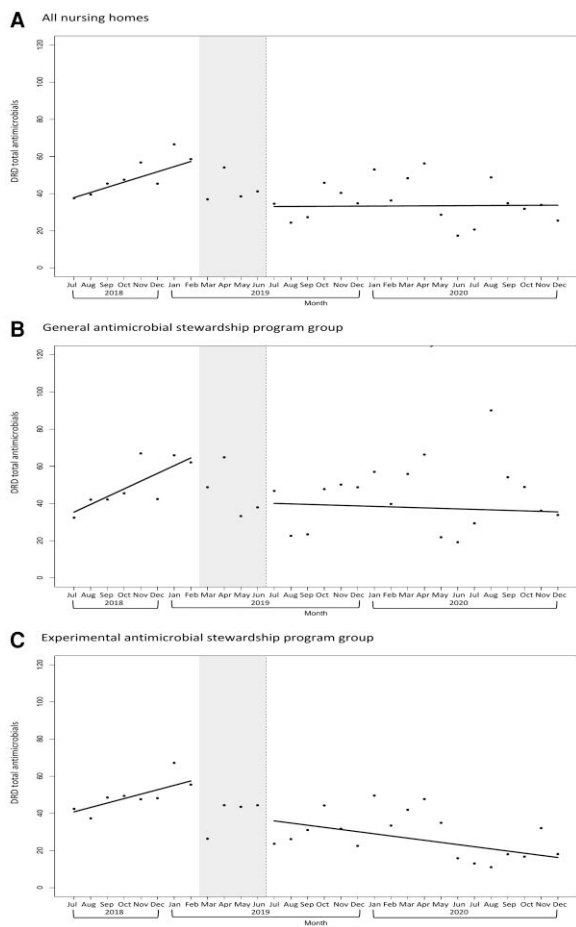
<sup>b</sup>Mean difference between groups in the intervention period.

## DISCUSSION

The results of this study suggest that a multimodal education-based ASP for NHs reduced total antibiotic consumption, specifically the consumption of quinolones and amoxicillin–clavulanic acid, reversing the increasing trends of the preintervention period, and that an ASP was associated with a decrease in the prevalence of MDRO among residents, without increasing hospitalizations caused by infections. However, the experimental ASP failed to achieve larger reductions in antibiotic consumption and MDRO prevalence compared with the general ASP. Previous studies have reported that ASPs appear to improve antimicrobial use in this setting, although not all results demonstrate a significant favorable impact of these programs [13–15]. Most studies analyzed changes in the number of prescriptions or, less frequently, in DRD as an internationally accepted measure of antibiotic use, as it was in our case. Whereas most studies have focused exclusively on UTIs [15, 22, 23] and, to a secondary extent, on RTIs [14], our ASP focused on all types of infectious syndromes, regardless of their etiology. Implementation of our education-based ASP was associated with higher rates of reduction in antibiotics than previously reported [14, 15, 22–26], with a significant 31.2% decrease (–16.72 DRD) in the overall use of systemic antimicrobials 1.5 years after initiation of the program. Of note, quinolones

were the antibiotics that showed the highest reduction (52.2%; –7.76 DRD), an outcome of particular interest considering the risks associated with their use in the elderly [4]. Interestingly, no “squeezing the balloon” phenomenon was detected [27]. Moreover, the incidence of hospital admissions due to infections remained unchanged, confirming the safety of the stewardship interventions in these centers. This is in line with previous studies [13–15] and suggests that educational ASPs can lead to a net reduction in antibiotic use and changes in prescribing behavior among NH doctors, with no risk of undertreating infections.

We expected that the use of 1-to-1 educational interviews as a core activity of an ASP embedded in a bundle of educational actions would have attained a further significant impact on consumption outcomes, as it has previously shown success in reducing antimicrobial prescribing in both hospitals and primary care settings [8, 9, 11]. In our study, the better results of the experimental group did not reach significant differences compared with the general group, except for azithromycin use. This was likely driven by the impact of the COVID-19 pandemic during the last year of the intervention, which was associated with an increase in overall average antimicrobial use of 40% and disruption of educational interviews during the pandemic waves. A recent study carried out in 1144 US NHs describes an



**Figure 2.** Interrupted time-series analysis of changes in trends of total antimicrobial use. Solid lines indicate baseline and intervention trends for the total use of antimicrobials in all nursing homes under study (A), in the general ASP group nursing homes (B), and in the experimental ASP group nursing homes (C). Gray area indicates phase-in period (4-month transition). Statistics are presented in the text and in [Supplementary Table 4](#). Abbreviation: DRD, defined daily doses per 10-00 resident days.

increase in prescribing of antibiotics commonly used for respiratory infections during the COVID-19 pandemic [28]. Our results suggest that the ASP reduced azithromycin use, even though it increased during the pandemic phase because of its presumed activity against severe acute respiratory syndrome coronavirus 2. This benefit was greater in the experimental ASP group than in the general ASP group, despite the fact that the number of clinical interviews decreased by 75% due to work overload during the pandemic period and that the first wave impacted the experimental ASP group NHs more intensely.

With the educational interviews carried out online, we evaluated a new training tool for ASPs in NHs, creating new opportunities for stewardship interventions in these facilities [29], which are located far from academic centers. It is noteworthy that the assessment of the educational interviews by the NHs doctors was excellent. On the basis of our previous studies

[9, 11] and findings of the present study, we think that regular and continuous performance of this training activity would be a useful tool for NHs to use more widely.

Although there is growing evidence of a favorable ecological impact of long-term stewardship interventions in hospital and community care settings [9, 11, 12], there is little information about the effect of ASPs on the incidence of infections caused by MDRO in NHs. In one study on this topic, the authors reported no reductions in the incidence of *Clostridioides difficile* and MRSA after 2 years of intervention [26]. In another study, *C. difficile* infection rates were lower in the intervention group [23]. The results from our study show an ecologically positive effect associated with the implementation of ASPs in NHs, significantly reducing the overall prevalence of MDRO colonization among residents (−7.3% age points) after the inception of the program. This reduction was mainly driven by the decrease in prevalence of ESBL *E. coli*, which starting at 14.3%, a value similar to 15.3% described in other European NHs [5], halved at the end line.

This study has several limitations. First, the limited number of clusters under study prevented us from making inferences for the general population, as the among-population variance accuracy may be compromised. In order to control this bias, we used random effects, restricted maximum likelihood estimation, and the Satterthwaite degrees-of-freedom correction to minimize the type I error in studies with small samples, allowing improved parameter estimation accuracy [30]. In addition to comparing estimated marginal means with LMM and due to the longitudinal nature of the data conforming time series, we performed an ITSA to evaluate changes in trends over time, a segmented regression approach known to be the most robust type of analysis to assess the impact of health interventions in longitudinal data [21]. Second, the unexpected onset of the COVID-19 pandemic could have minimized the effect of the interventions. We did not assess other factors such as differences in resident makeup over time, fewer NH admissions, changes in case mix, or the impact of dexamethasone in the treatment of COVID-19 that could have contributed to the reduction in antimicrobial consumption in addition to the ASP. However, the specific reductions observed for amoxicillin-clavulanic acid and fluoroquinolones reflect a general change in prescribing habits that is suggested to be a result of the ASP intervention [28]. Finally, changes in contact precautions, hand hygiene, wearing masks, increased awareness, and other secular changes in NHs during the COVID-19 pandemic may have influenced the reduction in the prevalence of MDRO in this study.

Our study also has strengths. It is a longitudinal study, which allowed us to assess the evolution of the outcomes over 30 time-series data points. Moreover, the ASP was not stopped because of the COVID-19 pandemic, a fact that enriched the knowledge

**Table 3. Effect of the Intervention on the Prevalence of Resistant Bacteria**

Nursing Homes Group	Baseline Period	Intervention Period	Difference <sup>a</sup> (95% CI)	P Value <sup>a</sup>	Intergroup Difference <sup>b</sup> (95% CI)	P Value <sup>b</sup>
<b>Total MDR bacteria</b>						
All NHs	24.7% (114/462)	17.4% (67/385)	-7.3% (-12.7 to -1.7)	.012	...	
Experimental ASP group	22.8% (41/180)	18.5% (32/173)	-4.3% (-12.7 to 4.2)	.38	2.0% (-5.6 to 9.8)	.71
General ASP group	25.9% (73/282)	16.5% (35/212)	-9.4% (-16.4 to -2.0)	.01		
<b>MDR-gram negative bacilli</b>						
All NHs	16.2% (75/462)	9.1% (35/385)	-7.1% (-11.6 to -2.5)	.002	...	
Experimental ASP group	10.6% (19/180)	8.7% (15/173)	-1.9% (-8.2 to 4.5)	.67	-8% (-6.5 to 5.3)	.92
General ASP group	19.9% (56/282)	9.4% (20/212)	-10.5% (-16.4 to 4.1)	.002		
<b>ESBL <i>Escherichia coli</i></b>						
All NHs	14.3% (66/462)	7.3% (28/385)	-7.0% (-11.1 to -2.8)	.001	...	
Experimental ASP group	8.9% (16/180)	8.1% (14/173)	-.8% (-6.8 to 5.2)	.92	1.5% (-7.2 to 3.8)	.72
General ASP group	17.7% (50/282)	6.6% (14/212)	-11.1% (-16.7 to -5.3)	<.0001		
<b>ESBL <i>Klebsiella pneumoniae</i></b>						
All NHs	0.6% (3/462)	1.8% (7/385)	1.2% (-4 to 3.1)	.19	...	
Experimental ASP group	0.6% (1/180)	0.6% (1/173)	.0% (-2.6 to 2.7)	1.0	-2.2% (-5.5 to .8)	.14
General ASP group	0.7% (2/282)	2.8% (6/212)	2.1% (-3 to 5.4)	.07		
<b>Carbapenem-resistant Enterobacterales</b>						
All NHs	0.0% (0/462)	0.0% (0/385)	.0% (-9 to .8)	1.0	...	
Experimental ASP group	0.0% (0/180)	0.0% (0/173)	.0% (-2.2 to 2.1)	1.0	.0% (-1.7 to 2.2)	1.0
General ASP group	0.0% (0/282)	0.0% (0/212)	.0% (-1.7 to 1.3)	1.0		
<b>MDR <i>Pseudomonas aeruginosa</i></b>						
All NHs	1.1% (5/462)	0.0% (0/385)	-1.1% (-2.5 to -.1)	.06	...	
Experimental ASP group	0.6% (1/180)	0.0% (0/173)	-.6% (-3.1 to -1.7)	0.99	.0% (-2.2 to 2.2)	1.0
General ASP group	1.4% (4/282)	0.0% (0/212)	-1.4% (-3.6 to -.6)	.06		
<b>MDR <i>Acinetobacter baumannii</i></b>						
All NHs	0.2% (1/462)	0.0% (0/385)	-.2% (-1.2 to .8)	0.99	...	
Experimental ASP group	0.6% (1/180)	0.0% (0/173)	-.6% (-3.1 to 1.7)	0.99	.0% (-1.8 to 2.2)	0.99
General ASP group	0.0% (0/282)	0.0% (0/212)	.0% (-1.8 to 1.3)	1.0		
<b>Methicillin-resistant <i>Staphylococcus aureus</i></b>						
All NHs	8.5% (39/458)	8.6% (33/384)	.1% (-3.7 to 4.0)	.92	...	
Experimental ASP group	12.3% (22/179)	9.8% (17/174)	-2.5% (-9.2 to 4.2)	.55	2.2% (-3.5 to 8.2)	.57
General ASP group	6.1% (17/279)	7.6% (16/210)	1.5% (-3.0 to 6.5)	.89		

Data are resistance percentage (%) (n/N).

Abbreviations: ASP, antimicrobial stewardship program; CI, confidence interval; ESBL, extended-spectrum  $\beta$ -lactamase; MDR, multidrug-resistant; NH, nursing home.

<sup>a</sup>Absolute percentage point difference between periods.

<sup>b</sup>Absolute percentage point difference between groups in the intervention period.

of the pragmatic effect of education-based ASPs under such unfavorable circumstances.

## CONCLUSIONS

This study suggests that a nonrestrictive multimodal ASP for NHs based on a bundle of 5 educational interventions reduces the total use of antimicrobials, improves the prescription profile, and is associated with a decrease in the prevalence of MDRO in the residents, with no deleterious effects on clinical outcomes. This trial did not find benefits associated with educational interviews, probably due to the COVID-19 pandemic.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted

materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

## Notes

**Author contributions.** J. M. C. conceived of, designed, and supervised the study; obtained public funding from the Institute of Health Carlos III; and reviewed the draft manuscript. J. M. C., G. P., J. C. C.-R., and A. B. G.-G. performed the scientific literature search. B. C.-A., B. R.-R., J. G.-M., M. I. G.-B., M. G.-M., M. D. S.-B., M. B. M.-R., M. R. C.-C., R. C. N.-P., M. A. E.-M., A. P.-B., I. M.-A., M. G.-F., M. R. M.-S., S. B.-R., and the PROA-SENIOR study group provided the data. C. M. R.-F. was in charge of registration and official authorizations. J. A. E.-T., M. V. G.-N., and J. A. L.-J. supervised the setup of the nursing homes, antimicrobial consumption, and microbiological networks. J. C. C.-R. was responsible for monitoring field, laboratory, clinical, and data management activities. A. R. V. and M. E. P.-I. performed the microbiological analyses. G. P. performed the statistical analysis. G. P. and A. B. G.-G. wrote the first draft of the manuscript. J. M. C., J. C. C.-R., A. R. V., and M. E. P.-I. revised the manuscript critically. All authors interpreted the data and read and approved the final manuscript. J. M. C. had full access

to all data in the study and had the final responsibility for the decision to submit for publication.

**Acknowledgments.** The authors acknowledge the invaluable contributions of all members of the antimicrobial stewardship program: doctors, nurses, and the rest of the staff of the participating long-term care facilities, and pharmacists and clinical microbiologists of the reference hospitals. They are grateful to Enrique Montero and Henry A. Andrade for their advice on the statistical analysis plan development and to nurses M. Mar Silva-Sánchez and Macarena López-Verdugo for their dedication and attention to the residents during the microbiological sampling. They thank the directors of the centers; the Consejería de Salud y Familias, Andalucía, Spain; and the Consejería de Igualdad, Políticas Sociales y Conciliación, Andalucía, Spain, for supporting implementation of the antimicrobial stewardship program.

**Disclaimer.** The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

**Financial support.** This work was supported by the Instituto de Salud Carlos III, the Spanish Ministry of Science and Innovation (grant PI17/02195), and was partially funded by the European Development Regional Fund "A Way to Achieve Europe".

**Potential conflicts of interest.** J. M. C. has received travel grants and honoraria as a speaker from Novartis, Astellas Pharma, Pfizer, MSD, Janssen Pharmaceuticals, and AstraZeneca outside the submitted work. A. R. V. has received honoraria as a speaker from Pfizer outside the submitted work. J. M. C. reports funding from Centro de Investigación Biomédica en Red de Enfermedades Infecciosas, Madrid, Spain. J. M. C., G. P., and J. C. C.-R. report grants from the Instituto de Salud Carlos III, Spanish Government, cofinanced by the European Development Regional Fund (A Way to Achieve Europe), and from the Spanish Network for Research in Infectious Diseases during the conduct of the study. A. B. G.-G. reports funding from the Subprograma Río Hortega and Juan Rodés, Instituto de Salud Carlos III, Ministerio de Ciencia e Innovación, Spanish Government. L. H.-H. reports funding from the Subprograma Río Hortega. M. E. P.-I. is a researcher funded by the program Nicolás Monardes, Servicio Andaluz de Salud, Junta de Andalucía, Spain. A. R. V. is supported by the Subprograma Juan Rodés, Instituto de Salud Carlos III, Subdirección General de Redes y Centros de Investigación Cooperativa, Ministerio de Ciencia, Innovación y Universidades, Spain. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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