Reduction in Antibiotic Use Following a Cluster Randomized Controlled Multifaceted Intervention: The Israeli Judicious Antibiotic Prescription Study

Gili Regev-Yochay,1,2*, Meir Raz,4 Ron Dagan,5 Hector Roizin,4 Benjamin Morag,4 Shmuel Hetman,4 Sigal Ringel,4 Neta Ben-Israel,4 Miriam Varon,4 Eli Somekh,2,4,6 and Ethan Rubinstein1,2,7

1Infectious Disease Unit, Sheba Medical Center, Ramat-Gan, Israel, 2Sackler Medical School, Tel-Aviv University, Tel-Aviv, Israel, 3Department of Epidemiology, Harvard school of Public Health, Boston, Massachusetts, 4Maccabi Healthcare Services, Hashfela District, Rishon Lezion, Israel, 5Pediatric Infectious Disease Unit, Soroka University Medical Center, and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel, 6Pediatric Infectious Disease Unit, Wolfson Medical Center, Holon, Israel, and 7Section of Infectious Diseases, University of Manitoba, Winnipeg, Manitoba, Canada

Background. Antibiotic overuse is of great public health concern. This study assessed whether intervention among physicians and their treated population could achieve a sustained reduction in antibiotic use, specifically in classes known to promote antibiotic resistance among children in a community setting.

Methods. We performed a cluster randomized controlled multifaceted trial among 52 primary care pediatricians and the 88,000 children registered in their practices. The intervention was led by local leaders and engaged the participating physicians. It included physician focus group meetings, workshops, seminars, and practice campaigns. These activities focused on self-developed guidelines, improving parent and physician knowledge, diagnostic skills, and parent-physician communication skills that promoted awareness of antibiotic resistance. The main outcome measure was the change in annual antibiotic prescription rates (APRs) of children treated by the intervention group physicians as compared with rates among those treated by control group physicians. The study comprised a 2-year pre-intervention period, a 3-year intervention period, and a 1-year follow-up period. Mixed-effect models were used to assess risk ratios to account for the clustered study design.

Results. A decrease in the total APR among children treated by the intervention physicians compared with those treated by the control physicians was observed in the first intervention year (APR decrease among control physicians, 40%; APR decrease among intervention physicians, 22%; relative risk [RR], .76; 95% confidence interval [CI], .75–.78). This reduction crossed over all antibiotic classes but was most prominent for macrolides (macrolide prescription rate among control physicians, 58%; macrolide prescription rate among intervention physicians, 27%; RR, .58; 95% CI, .55–.62). The effect was sustained during the 4 following years.

Conclusions. Multifaceted intervention that engages the physicians in an educational process is effective in reducing APRs and can be sustained.

Clinical Trials Registration. NCT01187758.

Antibiotic resistance in community-originating pathogens is an increasing threat [1] and therefore has been claimed by the Centers for Diseases Control and Prevention and the World Health Organization to be one of the most pressing public health problems (see http://www.cdc.gov/drugresistance/ and http://www.who.int/mediacentre/factsheets/). Multiple studies from various parts of the world have demonstrated a strong and consistent association between antibiotic use and antibiotic resistance, at both the individual and community levels.
Despite this evidence, excessive and inappropriate use of antimicrobial agents is still common [5, 7–9]. Nearly half of all children with an upper respiratory tract infection (URTI) receive antibiotics despite lack of efficacy in this setting [5, 10]. Factors contributing to nonjudicious antibiotic use include inadequate knowledge (by both physicians and patients), unreal expectations, real or perceived pressure by the patient or parent, inappropriate patient-physician communication, high work load, inadequate health care structure, cultural norms, and the physician’s fears, experience, and education [11–14].

Different strategies have been attempted to promote judicious antibiotic prescription [14–27]. Single strategies have frequently failed [16, 22–25]. Multifaceted interventions, in general, have been more successful [17, 18, 26, 27].

The aim of this study was to evaluate whether a multifaceted intervention focused at the physician level, based on physicians’ engagement with an educational process but also involving parents and children, could result in a long-standing reduction in antibiotic prescription rates (APRs) to children at the community level. The intervention was particularly aimed at reducing APRs of antibiotic classes known to be promoters of antibiotic resistance (namely, long-acting macrolides and oral cephalosporins) [28, 29].

METHODS

The study took place in primary care pediatric solo practices located in 7 major cities in the Central District Hashfela of Maccabi Healthcare Services (MHS), a major health maintenance organization (HMO) in Israel, from 2002 through 2005. MHS in this district serves a population of 350,000 persons, including ~100,000 children of 1,200,000 inhabitants. The population in this area consists mainly of middle-class Jewish persons.

We used a cluster randomized controlled design, with practices (pediatricians) as the unit of randomization and with intervention at both levels of pediatricians and their patients. This allowed us to assess the effect of the intervention on APRs at the 2 levels. Ethics approval was granted through the Sheba Medical Center Human Research Ethics Committee.

Recruitment and Randomization

Eighty-nine primary care pediatric solo practices were active in Hashfela District at the time of study initiation. Inclusion criteria were as follows: medium to large practices treating >800 children per year, with relatively high availability of the physician (ie, opening hours of >3 d/week and ≥15 h/week). Eligible physicians that agreed to participate were assigned to a control or intervention study group through use of stratified randomization. Stratifying variables included the practice location, practice size, and APR at baseline (years 2000–2001). Additional stratifying variables included the physician’s experience (defined by board certification) and country of medical education, since these factors were shown to be associated with APR in a preliminary analysis (Figure 1 and Table 1).

Study Period

Data were collected during a period of 6 years (April 2000 through March 2006) and included 2 pre-intervention years, 3 intervention years, and 1 post-intervention year.

Participants

All children <18 years old and registered at the participating practices (Figure 1) were included. The demographic characteristics and antibiotic purchase data of the study population at baseline are shown in Table 2. In this district the population is relatively stable, with no significant migration in or out of these cities. Movement of patients from one practice to another is relatively infrequent, partly because it imposes extra fees for the patient.

Out-of-Study Physicians

A post hoc analysis included an additional physician control group of 105 primary care pediatricians working in other MHS districts, matched by practice size to the study physicians. Analyses that included this group compared only crude data on APRs rather than age-adjusted and visit-adjusted rates, since individual APR data were not available for children treated by this group of physicians.

Physician Commitment to Intervention

The basic principle of the intervention design was to achieve full engagement of the intervention group physicians in the educational process as a means to achieve long-standing antibiotic prescription habit changes. After randomization, 5 physicians allocated to the intervention group were asked to serve as local leaders. Their selection was based on their leadership skills, low APR at baseline, and consent. They were recruited 3 months before initiation of the intervention and took part in preparing the intervention process. Commitment of the other physicians was ensured through active engagement in the process as described below. None of the involved physicians received any financial reward for participating in this study, nor was their contract with MHS affected by the study results.

Multifaceted Intervention

An initial 2-day interactive workshop (held at the beginning of year 1) focused on defining the determinants for nonjudicious antibiotic prescription and potential interventions to reduce nonjudicious prescription. A second workshop (held at the beginning of year 2) focused on parent-physician communication, and a third workshop (held at the beginning of year 3) focused on APR feedbacks. After the initial workshop, each participating physician joined one of the focus groups established during that workshop.

Data were collected during a period of 6 years (April 2000 through March 2006) and included 2 pre-intervention years, 3 intervention years, and 1 post-intervention year.

Participants

All children <18 years old and registered at the participating practices (Figure 1) were included. The demographic characteristics and antibiotic purchase data of the study population at baseline are shown in Table 2. In this district the population is relatively stable, with no significant migration in or out of these cities. Movement of patients from one practice to another is relatively infrequent, partly because it imposes extra fees for the patient.

Out-of-Study Physicians

A post hoc analysis included an additional physician control group of 105 primary care pediatricians working in other MHS districts, matched by practice size to the study physicians. Analyses that included this group compared only crude data on APRs rather than age-adjusted and visit-adjusted rates, since individual APR data were not available for children treated by this group of physicians.

Physician Commitment to Intervention

The basic principle of the intervention design was to achieve full engagement of the intervention group physicians in the educational process as a means to achieve long-standing antibiotic prescription habit changes. After randomization, 5 physicians allocated to the intervention group were asked to serve as local leaders. Their selection was based on their leadership skills, low APR at baseline, and consent. They were recruited 3 months before initiation of the intervention and took part in preparing the intervention process. Commitment of the other physicians was ensured through active engagement in the process as described below. None of the involved physicians received any financial reward for participating in this study, nor was their contract with MHS affected by the study results.

Multifaceted Intervention

An initial 2-day interactive workshop (held at the beginning of year 1) focused on defining the determinants for nonjudicious antibiotic prescription and potential interventions to reduce nonjudicious prescription. A second workshop (held at the beginning of year 2) focused on parent-physician communication, and a third workshop (held at the beginning of year 3) focused on APR feedbacks. After the initial workshop, each participating physician joined one of the focus groups established during that workshop.
Group 1: Local Guidelines for RTIs
Physicians in this group developed evidence-based guidelines for the diagnosis and management of URTI, fever, otitis media, pharyngitis, common cold, and pneumonia according to pediatric and infectious disease societies’ guidelines (http://www.cdc.gov/getsmart/specific-groups/healthcare-providers.html) [30–33].

Group 2: Improving RTI Diagnosis
Physicians in this group led a seminar on improving otitis

Table 1. Characteristics of the Physician (Cluster) Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention group (n = 26)</th>
<th>Control group (n = 24)</th>
<th>P a</th>
<th>Out-of-study group (n = 124)</th>
<th>P b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical experience</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) of pediatrics board certified physicians</td>
<td>22 (84.6)</td>
<td>21 (87.5)</td>
<td>.768</td>
<td>106 (85.8)</td>
<td>.874</td>
</tr>
<tr>
<td>Country of medical education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) of East European physicians</td>
<td>10 (38.5)</td>
<td>10 (41.7)</td>
<td>.817</td>
<td>25 (20.0)</td>
<td>.042 c</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>54.7 (8.5)</td>
<td>53.3 (5.7)</td>
<td>.501</td>
<td>55.1 (6.2)</td>
<td>.781</td>
</tr>
<tr>
<td>No. (%) of male physicians</td>
<td>18 (69.2)</td>
<td>17 (70.8)</td>
<td>.902</td>
<td>89 (71.7)</td>
<td>.798</td>
</tr>
<tr>
<td>Practice size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of registered patients per year (SD)</td>
<td>1,746 (911)</td>
<td>1,890 (664)</td>
<td>.529</td>
<td>1,584 (733)</td>
<td>.328</td>
</tr>
<tr>
<td>Practice availability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean time open, h/week (SD)</td>
<td>25 (1.4)</td>
<td>25 (1.5)</td>
<td>.999</td>
<td>27 (9)</td>
<td>.261</td>
</tr>
<tr>
<td>City, no. of physicians</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holon and Bat-Yam</td>
<td>12</td>
<td>10</td>
<td>.749</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Rishon and Rehovot</td>
<td>7</td>
<td>7</td>
<td>.856</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Lod and Ramle</td>
<td>2</td>
<td>2</td>
<td>.938</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Ashdod</td>
<td>6</td>
<td>5</td>
<td>.845</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Mean APR in prestudy period, no. of</td>
<td>78.0 (39)</td>
<td>73.8 (32.4)</td>
<td>.682</td>
<td>111.6 (63)</td>
<td>&lt;.001 c</td>
</tr>
<tr>
<td>prescriptions per 100 patient-years (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Physicians in the intervention and control groups in the following cities were compared with physicians in the out-of-study group in the following districts: Holon and Bat-Yam, Northern District; Rishon and Rehovot, Southern District; Lod and Ramle, Hasharon District; Ashdod, Jerusalem District (5 physicians) and Tel-Aviv District (36 physicians). APR, antibiotic prescription rate.

a Control group versus intervention group.
b Out-of-study group versus intervention group.
c Statistically significant result (P < .05).
media diagnostic skills and solicited immediate access to URTI diagnostic tools including radiography, complete blood count, and blood cultures.

**Group 3: Promoting Awareness of Antibiotic Resistance**
Physicians in this group distributed monthly or quarterly Hebrew-translated relevant abstracts from leading medical journals.

**Group 4: Antibiotics Only When Necessary**
Physicians in this group developed a campaign for parents and children who visited the study practices, which included posters, pamphlets, and coloring booklets based on materials prepared by the US Centers for Diseases Control and Prevention that were translated into Hebrew and adapted to local culture.

**Group 5: Parents as Partners**
Physicians in this group prepared a simulation seminar that focused on parent-physician communication and on physician leadership.

The major emphases throughout the intervention activities were (1) that antibiotics should be given only when bacterial infections are highly suspected (according to guidelines) and (2) that the drugs of choice for most indications are penicillin or amoxicillin and that other antibiotic classes (particularly macrolides and cephalosporins) further promote antibiotic resistance [28, 29] and should be avoided. Cost of the various antibiotics was deliberately disregarded.

The intervention was intensive during the first year, with many focus group meetings and quarterly seminars, and became gradually less intensive, with only 1 seminar and an annual workshop during the third (maintenance) year. The timeline of the intervention is shown in a Supplementary Figure (Figure 1; online only). Physicians in control practices had no trial intervention.

The primary outcome measure was annual APR, defined as the number of antibiotic prescriptions per 100 patient-years. Secondary outcome measures were specific antibiotic class prescription rates for the penicillin, macrolide, and cephalosporin classes.

Data from retail central pharmacies in the MHS network served as the source of antibiotic prescription data. Because over-the-counter antibiotics are prohibited in Israel and because antibiotics are significantly cheaper when purchased in HMO pharmacies, we believe that this is a close approximate of the true antibiotic use in the studied population. Individual patient antibiotic purchase data were available for the control and intervention groups, which allowed adjustment for patient age and number of visits. For the out-of-study group physicians, only crude data were available. Furthermore, data for the first 2 years (2001–2003) were not available for the out-of-study group (due to changing computer systems). We therefore conducted 2 separate analyses: the first only for control versus intervention, based on the individual patient data and adjusted accordingly, and a second analysis that included the out-of-study group, which assessed only crude data.

**Statistical Analyses**
Sample size estimation was based on preliminary data on APR at the baseline year and an intraclass correlation coefficient (ρ) of .065. To detect a 10% reduction in APR in a nonclustered design with 80% power at a 2-sided significance level of \( P < .05 \) and accounting for the design effect, a total of 37,760 participants would be needed in each arm, with 1,800 patients in each practice (cluster size), and at least 21 practices in each arm would be required.

Mixed-effect models were used for assessing change in APR, comparing intervention and control target populations, to account for the clustered study design: treated children (at level 1), clustered within their primary care physicians (at level 2). Multilevel Poisson regression analysis was chosen as the primary analysis method because the main objective was to estimate the community-specific change in antimicrobial use, while accounting for the clustered design. The outcome of interest was the number of antibiotic prescriptions per 100 patient-years. The main terms in the model were the control and intervention arms and the time period. The interaction terms of the study group over period X after the intervention were used to test the null hypothesis that the change over time in prescription in the intervention and control groups was equal.

Since the age of the child and the number of visits to the practice per year were strong predictors of APR, they were included in the model. However, inclusion of these variables did not influence the estimates of the intervention effect in any of the time periods because these variables were highly similar between the 2 groups.

For the analysis of the intervention effect at the physicians level, a Poisson regression was similarly used (but in a single level). To assess why 3 physicians in the intervention group did...
not change their prescription habits, we compared variables of these physicians to 10 matched controls. For these analyses, we used the Mann-Whitney test and Fischer exact test. The statistical software programs used were MLwin (version 2.0) and SAS (version 9.1).

RESULTS

Figure 1 shows the flow of participants and practices through the study. Fifty-two of the 60 eligible physicians agreed to participate and were assigned to either a control group or an intervention study group by use of stratified randomization. The mean practice size at baseline was 1,746 registered patients (SD, 911 patients) in the intervention group and 1,890 patients (SD, 664 patients) in the control group. Of 52 physicians, complete data (6-year follow-up) was collected and analyzed for 50; 1 physician died and another moved out of the region. Both belonged to the control group and dropped out during the first intervention year. Twenty-four (92%) of 26 intervention group physicians participated in >50% of 11 intervention activities and 17 (65%) of 26 participated in >80% of these activities.

Multifaceted Intervention

Although the study design did not enable us to measure the effect of each particular intervention facet, we specifically assessed the effect of the campaign. Parents’ wish for antibiotics in the precampaign period was compared with that during the campaign. A 47% decrease in parents’ wish for antibiotics was observed [34]. In addition, the enhanced availability of diagnostic tools did not have any effect on antibiotic use, since direct access to these tools was used very scarcely (3 times by a single physician).

Antibiotic Prescription Rates—Participant Level

During the baseline year (April 2000–March 2001), 44,453 children were seen by the control physicians and 43,677 children were seen by the intervention physicians. The rates of antibiotic drugs purchased by these populations are shown in Table 3.

Table 3. Number of Patients and Total Antibiotic Prescription Rate During the Study Period

<table>
<thead>
<tr>
<th>Study year (period)</th>
<th>Control group</th>
<th>Intervention group</th>
<th>Control group</th>
<th>Intervention group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients per year</td>
<td>No. of antibiotic prescriptions per 100 patient-years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (April 2000–March 2001)</td>
<td>44,453</td>
<td>43,677</td>
<td>76.32</td>
<td>78.38</td>
</tr>
<tr>
<td>1 (April 2001–March 2002)</td>
<td>45,195</td>
<td>44,702</td>
<td>70.95</td>
<td>65.57</td>
</tr>
<tr>
<td>2 (April 2002–March 2003)</td>
<td>45,918</td>
<td>42,495</td>
<td>59.34</td>
<td>46.93</td>
</tr>
<tr>
<td>3 (April 2003–March 2004)</td>
<td>48,023</td>
<td>46,046</td>
<td>57.58</td>
<td>48.18</td>
</tr>
<tr>
<td>5 (April 2005–March 2006)</td>
<td>47,701</td>
<td>49,998</td>
<td>54.56</td>
<td>45.91</td>
</tr>
</tbody>
</table>

During the second and third study years (in the year 2002), a general campaign for reducing antibiotic use was performed by MHS and coincided with our first intervention year. APRs were significantly reduced among the control group during this year by 22%; the intervention group showed a deeper reduction of 40% (relative risk [RR], .76; 95% confidence interval [CI], .75–.78; compared with the control group). The reduced prescription rate included all antibiotic classes but was most prominent for macrolides (58% and 27% reduction in the intervention and control groups, respectively; RR, .58; 95% CI, .55–.62).

The reduction achieved in the first year was sustained throughout the intervention period and during the follow-up year (2005–2006), with a persistent RR of ~.8 for total APR and cephalosporin prescription rate and a RR of ~.55 for macrolide prescription rate in the intervention group compared with rates in the control group (Figure 2 and Table 4). To assess whether the prescription rate reduction in the control group was due to intervention cross-contamination, we performed post hoc analyses of crude APRs that included an out-of-study group (Figure 3). The reduction in the control group was significantly greater than that in the out-of-study group, demonstrating some cross-contamination effect. The general campaign resulted in a substantial reduction in cephalosporin prescription rate (33.8%) (Figure 3B) but only a slight reduction in total APR (9.4%) (Figure 3A) and a nonsignificant decrease in macrolide prescription rate (1.1%) (Figure 3C).

Antibiotic Prescription Rates—Cluster (Physician) Level

At the physician level, the decreased overall prescription rate was significantly greater in the intervention group than in the control group (RR, .89; 95% CI, .81–.98). Macrolide prescription rates were most markedly reduced (RR, .65; 95% CI, .52–.81; intervention group vs control group); 20 (77%) of 26 intervention group physicians decreased macrolide use by >50%, compared with 2 (8%) of 24 control group physicians ($P < .001$). The penicillin prescription rate did not change significantly in either group. The cephalosporin prescription rate was reduced significantly but with no difference between the 2 groups.

Prescription rates by 3 physicians in the intervention group did not decrease. Moreover, macrolide prescription rates even increased among these physicians. We compared these high prescribers with 10 physicians who had similar initial prescribing rates (in the 30th–70th percentile) but found no difference in any of the variables (age, medical experience, board
certification, graduation from medical school in Israel, or years of experience). One of the 3 high prescribers showed low attendance in the intervention activities (participation in 3 of 11 activities), whereas the other 2 high prescribers showed high attendance (participation in 9 of 11 and 10 of 11 activities, respectively).

**DISCUSSION**

This randomized controlled study is unique in achieving significant and sustained APR reductions in a large pediatric population by implementing a long-standing, self-developed, multifaceted intervention strategy focused on the physicians. Most reported intervention studies either compared an intervention period with a historical period or did not include a control group [15, 19, 23, 26, 35, 36]. Well-designed community-based studies have either failed to achieve significant reductions in APRs [18, 20, 37–39] or shown modest reductions measured only over a relatively short period [20, 27, 39, 40].

The major novelty of this multifaceted intervention study was the emphasis on physician engagement and commitment to the educational process. This was achieved by enhancement and coaching that persuaded the physicians to take active part in the intervention. While the local leaders led the process, each of the participating physicians played an active role. Although we defined the study as a 3-year intervention, actually only the first year was intensive whereas the following years could be perceived as maintenance years. Another important novelty of this intervention was that in addition to the message to reduce unnecessary antibiotic treatments, part of the focus was on the significance of reducing treatments with antibiotic classes that in many cases do not represent a better solution than the penicillins [41], but may particularly promote antibiotic resistance, namely, macrolides and cephalosporins [28, 29].

**Table 4. Risk Ratios for Antibiotic Prescription Rate by the Intervention Group Population, Compared With the Control Group**

<table>
<thead>
<tr>
<th>Study year (period)</th>
<th>Total antibiotic use, RR (95% CI)</th>
<th>Penicillin use, RR (95% CI)</th>
<th>Cephalosporin use, RR (95% CI)</th>
<th>Macrolide use, RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (April 2000–March 2001)</td>
<td>1.116 (.91–1.36)</td>
<td>1.088 (.89–1.34)</td>
<td>1.129 (.87–1.47)</td>
<td>1.245 (.87–1.77)</td>
</tr>
<tr>
<td>1 (April 2001–March 2002)</td>
<td>.914 (.89–.93)</td>
<td>.888 (.86–.91)</td>
<td>.923 (.87–.98)</td>
<td>.975 (.93–1.02)</td>
</tr>
<tr>
<td>2 (April 2002–March 2003)</td>
<td>.765 (.75–.78)</td>
<td>.840 (.82–.87)</td>
<td>.772 (.73–.82)</td>
<td>.584 (.55–.62)</td>
</tr>
<tr>
<td>3 (April 2003–March 2004)</td>
<td>.809 (.79–.83)</td>
<td>.907 (.88–.93)</td>
<td>.895 (.83–.96)</td>
<td>.546 (.53–.59)</td>
</tr>
<tr>
<td>4 (April 2004–March 2005)</td>
<td>.809 (.79–.83)</td>
<td>.907 (.88–.93)</td>
<td>.785 (.73–.84)</td>
<td>.546 (.52–.57)</td>
</tr>
<tr>
<td>5 (April 2005–March 2006)</td>
<td>.844 (.82–.86)</td>
<td>.962 (.93–.99)</td>
<td>.767 (.71–.82)</td>
<td>.552 (.52–.58)</td>
</tr>
</tbody>
</table>

**NOTE.** CI, confidence interval; RR, relative risk.
In previous studies, the decrease in antibiotic use was most pronounced for β-lactam and was frequently accompanied by a simultaneous increase in long-acting macrolide prescription rate [36, 42]. The considerable success in reducing the macrolide prescription rate in our study was probably a result of the educational effort that led to physicians' comprehension of why and how macrolides promote antibiotic resistance.

Sustained behavioral changes such as prescription habits are difficult to achieve [43, 44]. Our main assumption was that such changes can be better accomplished if the drive to change becomes part of the physician's wish to improve his or her professional standards and deliver better medical care.

In this randomized controlled trial, 3 points of reference were used: the baseline APR, the randomized control group APR at the same time point, and the out-of-study group APR. This allowed us to determine the net intervention effect.

The decrease in total APRs during the first intervention year (2002–2003) may be at least partly explained by the general nationwide campaign carried out by MHS, since it was also observed to some degree in the control and out-of-study groups. Furthermore, a recent study reported a small but significant decrease in antibiotic use in a population insured by another HMO in Israel (Clalit Health Services) during these years [45]. However, the nationwide campaign did not particularly advocate macrolide reduction, and thus while the decrease in cephalosporin prescription rates was evident in the 2 control groups, macrolide prescription rates did not decrease in the out-of-study group and decreased only slightly in control group, as compared with 50%–60% reduction in the intervention group.

The significant decrease in prescription rates among physicians in the control group compared with rates in the out-of-study group is suggestive of cross-contamination, that is, indirect effect of the intervention on the control group to some degree. Indeed, the physicians in both groups practiced in the same district, attended common meetings, and had social interactions. Furthermore, surveys for carriage of antimicrobial-resistant pathogens took place among both intervention and control physicians during the study period, potentially inducing awareness of the fact that an antibiotic resistance intervention was taking place.

The out-of-study control group should have served as the reference group to report the RR of the intervention effect. However, because only crude data were available for this group, we performed a conservative analysis using the control group as our reference for RR calculation.

The fact that this study was prolonged allowed us to observe the sustained intervention effect. To achieve adjusted, unbiased results, we used multilevel analysis that accounted for the clustering by physician and city.

This study has several limitations. First, we were unable to isolate the effect of each component in the multifacet intervention and thus could not determine whether all components were necessary to achieve the current results. However, at least 1 of the components (increased availability of diagnostic tools) played no role, since physicians did not make use of this presumed advantage, whereas the clinic campaign in itself played some role [34]. Second, although we promoted judicious antibiotic prescription, we measured APRs and not how judicious the prescriptions were. However, the fact that most prescription reduction was observed with macrolides, which are rarely indicated as first-line treatment, strongly suggests that the intervention did improve judicious antibiotic prescription. Third, the intervention arm included only 26 physicians, and the feasibility of performing such an intervention in a larger scale or...
in other health delivery systems cannot be concluded from our study. However, the fact that such a significant reduction is possible should encourage health educators and public health leaders to undertake such trials in different countries with different cultures and different patient populations.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Acknowledgments

We greatly acknowledge all the members of the Israeli Judicious Antibiotic Prescription (IJAP) study group, without whose full cooperation and devotion this study could not have been performed. We also acknowledge Sara Nov and Estela Deraznez for help in data management, the team from the Department of Quality Management in Health Care of MHS, and particularly Irene Levinhoff, Orna Shemtov and Itzik Levy for leading the parent-physician communication component of the intervention, Rinat Cohen for assistance with the intervention, and Mimi Shraga and the study coordinators for their dedicated work.


Role of the funding source

The funding agencies had no role in designing the study, collecting the data, data analysis, interpretation of the data, writing the report or in the decision to submit the paper for publication. The protocol of the study can be accessed through http://www.clinicaltrials.gov.

Financial support

This work was supported by the Israel National Institute for Health Policy and Health Services Research (NIHP); and by Maccabi Healthcare Services (MHS).

Potential conflicts of interest

All authors: no conflicts.

Potential conflicts of interest

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 in the Acknowledgments section.

References


