RESEARCH

Impact of Antibiotic Administrative Restrictions on Trends in Antibiotic Resistance

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ABSTRACT

Context: In March 2001, in response to concerns about increasing resistance to fluoroquinolone (FQ) antibiotics, the Ontario Drug Benefit (ODB) program limited reimbursement of FQs to ODB beneficiaries defined as high risk or in whom other therapies are not tolerated.

Objective: To analyze the impact of the limited use (LU) policy changes on antibiotic resistance rates in Ontario, focussing on community-acquired pathogens.

Design: Ontario data submitted to the Canadian Bacterial Surveillance Network (CBSN) between January 1, 1998 and June 30, 2002 were analyzed for rates of resistance in various pathogen-antibiotic combinations. The effect of the LU policy on the level and rate of change of antibiotic resistance was estimated using time series models.

Results: Resistance rates for *S. pneumoniae* were 10-12% for penicillin, erythromycin and trimethoprim sulfamethoxazole (TMP/SMX) and less than 3% for amoxicillin and all three FQs tested. There was a statistically significant increasing trend in resistance rates of *S. pneumoniae* to amoxicillin and levofloxacin throughout the study period. Antibiotic resistance of *S. pneumoniae* to ciprofloxacin indicated a statistically significant decreasing trend over the study period with a statistically significant increase in the level of antibiotic resistance at the time of the LU policy implementation. No other indication of any statistically significant decrease in resistance rates associated with the LU policy was found.

Conclusions: Although no direct cause and effect can be proven with these observational data, there is no evidence that the limited use policy to restrict fluoroquinolones decreased antibiotic resistance in any of the pathogen-antibiotic combinations tested.

MeSH terms: Anti-bacterial agents; health policy; statistical models; reimbursement mechanisms; antibiotic resistance; drug resistance

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Antibiotics are a powerful treatment for infections, but pathogen resistance to these medications continues to increase.[1] Rising rates of antimicrobial resistance are viewed by the Public Health Agency of Canada as a major health care issue both in the community and hospital settings.[2,3] Recent North American studies[4-6] on antibiotic resistance have confirmed this, reporting increasing levels in antibiotic resistance of respiratory pathogens (*S. pneumoniae* and *H. influenzae)* due to a number of factors, including overuse and misuse of antibiotics.

Fluoroquinolones (FQ) are broadly accepted for the treatment of many infections because of their excellent pharmacokinetic properties and antimicrobial activity, and low incidence of side effects.[7] It is likely that FQs will be used more frequently in the future because of the emergence of resistance to other first- and second-line antimicrobial agents in common respiratory pathogens. Reduced pneumococci susceptibility to FQs remains low in Canada, but concerns were raised in response to the report by Chen et al. of increasing rates (from 0% in 1993 to 1.7% in 1997/1998) associated with increased FQ use.[4] Several studies have shown that reduced use of selected antibiotics decreased or slowed down antibiotic resistance in jurisdictions that adopted similar limited use policies.[2,8-12] In other reports, the reduced or complete cessation of the use of an antibiotic did not reduce the rate of antibiotic resistance.[8,13]

The Ontario Ministry of Health and Long-Term Care modified the coverage of specific antibiotics in March 2001 to address "the morbidity, mortality, and financial costs of multiple-drug-resistant infections for which there are few or no effective therapies" and reduce antibiotic resistance.[14] Specifically, reimbursement of the FQ antibiotics ciprofloxacin and ofloxacin was limited to Ontario Drug Benefit (ODB) program beneficiaries who met specific clinical conditions and risk factors (Table I), a restriction known as "Limited Use" (LU). The major listing changes were for two FQ antibiotics. Previously, reimbursement of these drugs was unrestricted, or in the ODB lexicon, "General Benefit" (GB). Levofloxacin, which was already listed as LU, had additional restrictions placed on its use. Norfloxacin, however, remained as GB because it was assumed that it was being

TABLE I

Ontario Drug Benefit (ODB) Formulary – Major Listing Changes, Effective March 2001[14]

Antibiotic Class and Agent	Former Listing	Current Listing	Reimbursement Restrictions Limited to the Treatment of Patients with:
Fluoroquinolones			
Ciprofloxacin Ofloxacin	GB*	LU†	Skin/soft tissue and bone/joint infection due to gram negative bacteria; genitourinary tract infection; chronic obstructive pulmonary disease with risk factors‡; gastrointestinal indications; step-down therapy after parenteral therapy of emergency department discharge; exceptional cases of allergy or intolerance to all other appropriate therapies.
Levofloxacin†	LU	LU§	Community-acquired pneumonia with co-morbid illnesses or failure to first-line therapy; chronic obstructive pulmonary disease with risk factors‡; step-down therapy after parenteral therapy of emergency department discharge; exceptional cases of allergy or intolerance to all other appropriate therapies.
Norfloxacin	GB	GB	
Macrolides			
Azithromycin||	GB	GB	
Clarithromycin||	GB	GB	
Penicillins			
Amoxicillin/clavulanic acid||	GB	GB	

* GB: General Benefit Listing Status
† LU: Limited Use Listing Status
‡ Risk factors include: poor pulmonary lung function, age over 65 years, comorbid medical illness (congestive heart failure, diabetes, chronic renal failure, chronic liver disease), chronic corticosteroid use, malnutrition, prolonged duration of disease, or four or more exacerbations per year.
§ With additional prescribing restrictions.
|| Continue to be listed as GB products, and listing status will be reassessed in one year.

used appropriately and it represented the best value-for-money in this class for treatment of urinary tract infections. Other antibiotics for which there was some concern about increasing resistance, such as clarithromycin, azithromycin and amoxicillin/clavulanic acid, remained as GB products. However, the use and resistance patterns of these macrolides were to be reassessed in one year's time.[14] This study analyzed the impact of the LU policy changes in Ontario on antibiotic resistance rates, focussing on antibiotic resistance for pathogens associated with community-acquired pneumoniae (CAP) including *S. pneumoniae*, *H. influenzae*, and group A streptococcus.

METHODS

Data source

Antibiotic resistance data were obtained from the Canadian Bacterial Surveillance Network (CBSN) and the Ontario Group A Streptococcal Study (OGASS). CBSN is an active antibiotic surveillance system that collects all sterile site isolates and a sample of 20 consecutive non-sterile site isolates of *S. pneumoniae* annually from participating centres across Canada: between January 1, 1998 and June 30, 2002, 4,765 isolates from Ontario were submitted. CBSN also collects 10-30 (depending on laboratory size) consecutive *H. influenzae* isolates (all types, including nontypable and Hib) from each participating site annually: between January 1, 1998 and June 26, 2002, 761 isolates were submitted. OGASS collects all sterile site isolates of *Streptococcus pyogenes* identified in Ontario laboratories: between January 1, 1998 and December 31, 2001, 1,210 isolates were submitted. Three pathogen datasets were analyzed: *S. pneumoniae* (penicillin, amoxicillin, erythromycin, levofloxacin, ciprofloxacin, moxifloxacin, and trimethoprim sulfamethoxazole (TMP/SMX)), *H. influenzae* (ampicillin), and group A streptococcus (erythromycin) (Table II). Since resistance to macrolides is class specific, erythromycin was selected as the representative of the class of macrolides.

Antibiotic susceptibility testing for all isolates is performed and interpreted using National Committee for Clinical Laboratory Standards methodology.[15] Resistance of *H. influenzae* to ampicillin was determined by the presence of β-lactamase production.[15] Since there are no ciprofloxacin breakpoints for *S. pneumoniae*, the minimal inhibitory concentration used to define *S. pneumoniae* as non-susceptible to ciprofloxacin for this study was ≥2 μg/mL.[5]

Analytical methods

Data were collected on 38 monthly observations prior to the March 1, 2001 introduction of LU, and 17 and 10 monthly observations thereafter, respectively, for the CBSN data and the OGASS data. Plots of the monthly resistance rates were visually inspected to identify any obvious changes in patterns before and after the LU policy change.

Autoregressive integrated moving average (ARIMA) time series models were estimated if autocorrelation was detected in the data; otherwise the model was estimated using Poisson regression.[16] Each data series was examined for autocorrelation using the white noise test.[16] Poisson regression is commonly used to model counts of rare events because all predictions from the model are non-negative, and moreover, the model accounts for the fact that resistance rates (number of isolates resistant/number of isolates tested) vary with the number of laboratory tests.[17] The models allowed the impact of the LU policy to affect both the level of resistance and the rate of change of resistance over time* and included all statistically significant ($p<0.05$) changes in antibiotic resistance throughout the study period (breakpoints)†, a linear variable representing

* For Poisson models, a linear variable representing time was included in the model along with the LU policy implementation indicator variable. The general form of the Poisson model was $Y_t=\alpha+\beta_1 \leftrightarrow Month+\beta_2 \leftrightarrow LU+\beta_3 \leftrightarrow Month \leftrightarrow LU+\varepsilon_t$. This model allows the impact of the LU policy to change both the level of resistance (through the LU term) and the rate of change of resistance over time (through the Month x LU term).

† A breakpoint was considered significant only after a Bonferroni adjustment to the significance level ($p=0.01$).[8,18] The final models included any significant breakpoints (found through breakpoint analysis, or the LU timepoint), a linear variable representing month of observation, and interactions between the breakpoint and time variables.

TABLE II

Antibiotic/Pathogen Combinations Tested from CBSN Database, Ontario Subset

Antibiotic Tested Timeframe	Pathogen *S. pneumoniae* 1998-2002 (# isolates = 4765)	Pathogen Group A streptococcus 1998-2001 (# isolates = 1210)	Pathogen *H. influenzae* 1998-2002 (# isolates = 761)
Penicillins			
Penicillin	X		
Ampicillin			X
Amoxicillin	X		
Macrolides			
Erythromycin	X	X	
Fluoroquinolones			
Levofloxacin	X		
Ciprofloxacin	X		
Moxifloxacin	X		
Others			
TMP/SMX	X		

Note: X indicates that resistance to the antibiotic was evaluated for the specified pathogen.

TABLE III

CBSN Database – Impact of LU Policy on Antibiotic Resistance by Antibiotic-Pathogen Combination

Antibiotic-Pathogen combination	Percentage Resistance at Jan 1998; June 2002	Estimated Impact of LU Policy (Implemented March 2001)	Trend Over Time (Independent of LU policy)
S. pneumoniae			
Beta-lactams			
Penicillin	12.4%; 12.4%	NS	NS
Amoxicillin	0.3%; 1.1%	NS	Increasing*
Macrolides			
Erythromycin	11.7%; 11.7%	NS	NS
Fluoroquinolones			
Levofloxacin	0.3%; 2.0%	NS	Increasing*
Ciprofloxacin**	2.3%; 2.0%	1.5%*	Decreasing*
Moxifloxacin	0.4%; 0.4%	NS	NS
Other			
TMP/SMX	10.3%; 10.3%	NS	NS
H. influenzae			
Beta-lactams			
Ampicillin	26.9%; 26.9%	NS	NS
group A streptococcus			
Macrolides			
Erythromycin	7.4%; 7.4%	NS	NS

NS – not statistically significant
* $p<0.05$
** There was a statistically significant increase (1.5%) observed in the rate of resistance of ciprofloxacin to *S. pneumoniae* at the LU policy implementation date. Please see text for further discussion.

month of observation and any statistically significant ($p<0.05$) interactions between breakpoints and time.

RESULTS

In January 1998, resistance rates for *S. pneumoniae* to penicillin, erythromycin and TMP/SMX were in the range of 10-12%, and less than 3% to amoxicillin and all three fluoroquinolones tested (Table III). Resistance for group A streptococcus to erythromycin was about 7% and for *H. influenzae* to ampicillin was close to 27%. By June 2002, increases were observed for amoxicillin (to 1.1%) and levofloxacin (to 2.0%).

The LU variable was statistically significant ($p<0.05$) in the regression model for antibiotic resistance of *S. pneumoniae* to ciprofloxacin, indicating an increase in the level of resistance by March 2001. No other model had a statistically significant result with respect to the LU policy variable (Table III, Figure 1). No statistically significant breakpoints were found in any of the models.

Resistance rates for *S. pneumoniae* demonstrated a statistically significant underlying trend over the study period for some antibiotics, independent of the LU policy. Resistance rates to amoxicillin and levofloxacin were increasing, while rates for ciprofloxacin were decreasing (Table III, Figures 1 and 2). There was no statistically significant underlying trend in resistance rates of *H. influenzae* to ampicillin or group A streptococcus to erythromycin.

DISCUSSION AND CONCLUSIONS

Restricting the use of specific antibiotics may result in both intended and unintended consequences – a phenomenon referred to by Burke et al. as 'squeezing the balloon'.[19,20] This emphasizes the need to evaluate the impact of policy restrictions such as restricting the reimbursement of fluoroquinolones, since the result may change the appropriate use of antibiotics, the overall use of antibiotics, and bacterial resistance rates. We reported previously that the limited use policy was associated with a decrease in FQ use that was offset by an increase in the use of other antibiotics, and resulted in no statistically significant change in the total number of antibiotic prescriptions.[21]

The health authorities acknowledged concern about an unintended increase in use and resistance to macrolides that could result from the introduction of the LU policy in Ontario.[14,22-24] Although no direct cause and effect can be proven with these observational data, there is no evidence that the LU policy restricting FQs decreased antibiotic resistance during the 17-month post-policy period in any of the antibiotic-pathogen combinations examined in this study. The methods used to analyze these data were robust and appropriate for rare event outcomes (such as antibiotic resistance). The models accounted for time so that the change in antibiotic resistance rates could be interpreted in the context of the overall patterns of antibiotic resistance before and after the policy change.

The pattern of antibiotic resistance displayed by *S. pneumoniae* to ciprofloxacin was curious. These data suggested an increase (versus a decrease) in level of ciprofloxacin resistance by March 2001, with an underlying statistically significant decreasing trend over the study period. This pattern is not congruent with plausible clinical explanations, and it is unlikely that this increase is related to the LU policy implementation. Part of the explanation may be the small number of observations of *S. pneumoniae* resistance to ciprofloxacin reported during this time period.

There are several limitations of this study. ODB is the largest drug plan in Ontario, accounting for 40% of all prescription drug spending, and covering over

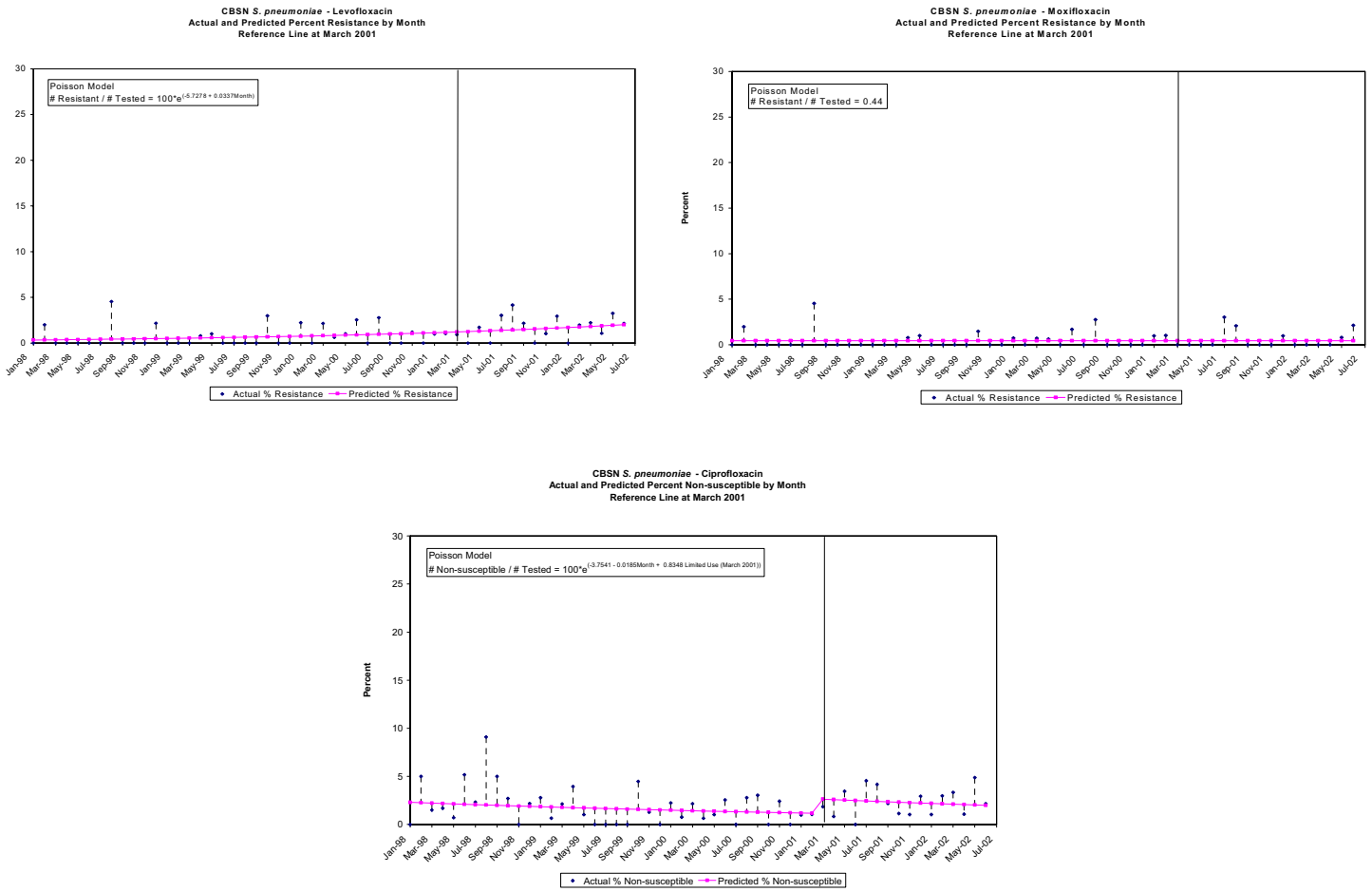

Figure 1. CBSN *S. pneumoniae* – percent resistance for fluoroquinolones

2.15 million claimants annually. The LU policy applies to all ODB beneficiaries (persons 65 years of age or older or receiving social assistance or specific care services in the province of Ontario) but its effect may be diluted because a significant proportion of the Ontario population was not directly affected by this administrative restriction.

The relationship between an administrative restriction and antibiotic resistance is complex, and it would have been preferable to study trends over a longer term spanning at least two full years, since use is partly a seasonal phenomenon. Based on the results from a study in Finland, where the rate of group A streptococcus resistance declined after two years of reduced macrolide use,[11] it is plausible that the 17-month follow-up period following the introduction of the LU policy is a sufficient amount of time to capture consequent changes in antibiotic resistance. Although we tested for other statistically significant changes in patterns over time through the breakpoint analysis and found none, this does not rule out the possible impact of other influences that may have occurred during the same time period. For example, data from the United States have shown a decrease in antibiotic-resistant *S. pneumoniae* associated with coverage of the pneumococcal vaccine Prevnar®.[25]

It should also be noted that a statistically significant change in resistance may not be clinically significant, or conversely, that even small changes in some resistance rates may be of clinical concern. In general, small changes in FQ resistance are considered clinically more noteworthy than for other antibiotics because resistance to fluoroquinolones develops slowly, requiring concurrent alterations in two genes.[26] The low but increasing prevalence of FQ resistance in Canada was a factor in the decision to limit the use of FQs.[4] In contrast, rates of resistance reported for *S. pneumoniae* to some penicillins and macrolides are tenfold that of FQ resistance rates. Using the Canadian Bacterial Surveillance Network data from 2000, 12.4% of *S. pneumoniae* isolates were not susceptible to penicillin.[5] In the same isolates, the resistance rates among macrolides, levofloxacin, gatifloxacin, and moxifloxacin were 11.1%, 0.9%, 0.8%, and 0.4% respectively.[5] Similarly, Doern et al. reported overall rates of *S. pneumoniae* resistance to the macrolides, tetracycline, chloramphenicol, TMP/SMX and clindamycin of 13%, 10%, 5%, 23% and 3%, respectively using the SENTRY Antimicrobial Surveillance Program data from 1998.[6]

Community-acquired pneumonia is one of the most common indications for the use of the antibiotics affected by the LU policy changes in Ontario. The CAP treatment guidelines issued by various professional societies (the Infectious Diseases Society of America[27] and the Canadian Infectious Disease Society and Canadian Thoracic Society[27,28]) currently recommend macrolides and beta-lactams as first-line agents for antimicrobial therapy. FQs, alone or in combination with other anti-

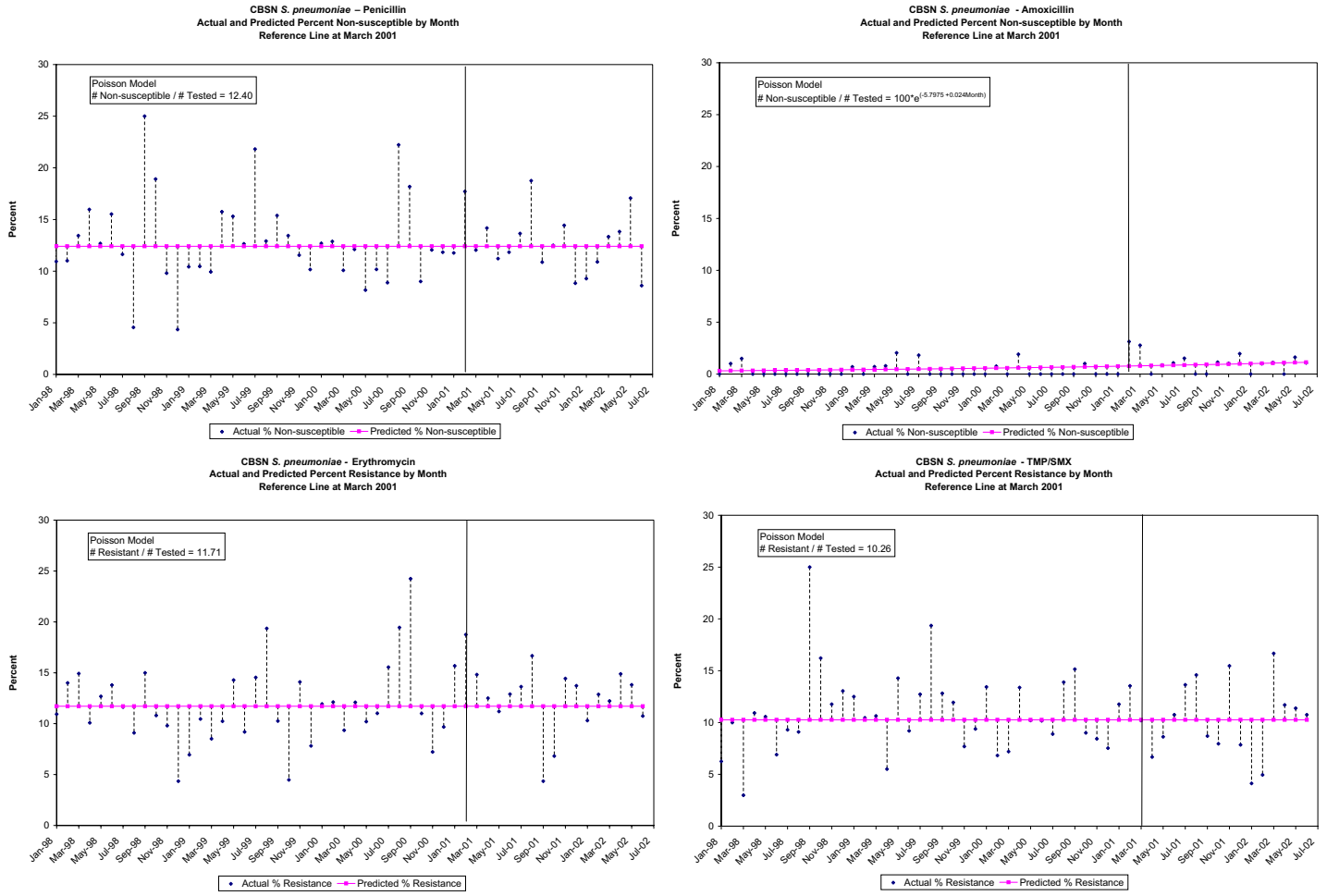

Figure 2. CBSN *S. pneumoniae* – percent resistance for penicillin, amoxicillin, erythromycin, and TMP/SMX

infectives, are generally accepted as the alternative if the recommended first-line agents fail. Due to their excellent safety and tolerability, the fluoroquinolones have become popular alternatives to penicillin and cephalosporin derivatives in the treatment of various infections, including respiratory infections.[7] The challenge will be to use these agents wisely to prevent the widespread emergence of FQ resistance. This will require balancing the use of antibiotics to which resistance is more common in order to preserve a new class for serious infections in the longer term (something policy-makers may wish to do) and using an antibiotic to which it is certain that the patient's isolate is susceptible (something individual physicians and patients may wish to do). As resistance rates for other antibiotics rise, clinicians will need to consider closely guideline recommendations, and the expected clinical benefits and risks of prescribing alternatives. In this context, continued assessments are important to evaluate the impact of policy changes on prescribing patterns, appropriate use of antibiotics, and trends in antibiotic resistance.

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RÉSUMÉ

Contexte : En mars 2001, en réponse aux préoccupations soulevées par la résistance accrue aux fluoroquinolones (FQ), le Programme de médicaments de l'Ontario limitait le remboursement de ces antibiotiques aux seuls bénéficiaires qui présentent un risque élevé ou qui ne tolèrent pas d'autres thérapies.

Objectif : Analyser l'impact du changement d'orientation en faveur de l'usage limité (UL) sur les taux d'antibiorésistance en Ontario, en mettant l'accent sur les agents pathogènes acquis dans la communauté.

Conception : Nous avons analysé les données ontariennes introduites dans le Réseau canadien de surveillance des bactéries (RCSB) entre le 1er janvier 1998 et le 30 juin 2002 pour obtenir les taux de résistance de diverses combinaisons d'agents pathogènes et d'antibiotiques. Nous avons évalué l'effet de la politique d'UL sur les niveaux et sur le taux de changement de l'antibiorésistance à l'aide de modèles en séries chronologiques.

Résultats : Les taux de résistance à *S. pneumoniae* variaient entre 10 % et 12 % pour la pénicilline, l'érythromycine et le triméthoprime-sulfaméthoxazole (TMP/SMX) et se situaient à moins de 3 % pour l'amoxicilline et les trois FQ testées. Nous avons observé une tendance à la hausse statistiquement significative dans les taux de résistance de *S. pneumoniae* à l'amoxicilline et à la lévofloxacine pendant toute la période d'étude. L'antibiorésistance de *S. pneumoniae* à la ciprofloxacine présentait une tendance à la baisse statistiquement significative sur la période d'étude, ainsi qu'une hausse significative du niveau d'antibiorésistance lors de la mise en œuvre de la politique d'UL. Aucune autre indication d'une baisse significative des taux de résistance associés à la politique d'UL n'a été relevée.

Conclusions : Ces données d'observation ne permettent pas de prouver l'existence d'un lien causal direct, mais rien n'indique que la politique d'usage limité des FQ a diminué l'antibiorésistance dans les combinaisons d'agents pathogènes et d'antibiotiques testées.