Rapid reduction in hospitalizations after an intervention to manage severe asthma

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4. Sponsors:
Fundação de Amparo a Pesquisa da Bahia (FAPESB), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Brazil; and Social Change, Asthma and Allergy in Latin America (SCAALA) project - Welcome Trust, United Kingdom. The role of the sponsors was to provide scholarships for postgraduate students and faculty members, to cover expenditures incurred with administration and training in ProAR. They had no role in data management or analysis, neither in the preparation of this report.

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Abstract

Asthma is the third cause of hospitalizations due to clinical illnesses in Brazil. The Programme for Control of Asthma in Bahia (ProAR) leads an intervention in Salvador City - Brazil to manage severe asthma for free. The aim of this study was to identify trends in asthma hospitalization in the entire City and to evaluate the impact of ProAR.

Information on asthma hospitalizations from 1998 to 2006 was collected. We analyzed trends in Salvador (2.8 million inhab.) before and after ProAR, taking pneumonia and myocardial infarction for local comparison. For an external control we took information on asthma from Recife, which is the most comparable Brazilian city.

In Salvador, asthma hospital admissions declined by 82.3% (1998-2006). A greater proportion of this reduction (74%) happened after 2003, in parallel to the implementation of ProAR. The reduction in asthma admissions in Recife was smaller. The rates of hospitalization in 2006 were: 2.25/10,000 inhab. in Salvador and 17.06 in Recife. In Salvador, we found an inverse correlation between provision of medication for asthma and hospitalization (- 0.801; p <0.0001).

A rapid reduction in asthma admissions in the entire City of Salvador was associated with ProAR, a public health intervention targeting severe asthma.

Word count: 200

Key words: asthma, hospitalization, prevention, treatment.

Short title: Rapid reduction in asthma hospitalizations.
Introduction

Asthma, a very common disease, is associated with the need for emergency room visits, risk of hospitalizations and deaths. Asthma exacerbations due to uncontrolled disease place a considerable burden on the health care system, in particular in developing countries. In Latin America some 34 millions of individuals have asthma. In Brazil, symptoms of asthma are found in 20% of the adolescents and asthma is the third cause of hospitalizations among all clinical illnesses.

Secondary prevention using inhaled medication can reduce asthma exacerbations. A successful Finnish National Asthma Control Program markedly reduced asthma morbidity and mortality. In Brazil and many Latin American countries there is no implementation of national strategies for asthma prevention or outpatient management. Isolated non-standardized initiatives restricted to a few cities and focused on distinct ages and asthma severity groups have been implemented.

The combination of a high prevalence of asthma and limited access to secondary prevention may have led to elevated morbidity and unacceptable mortality in Brazil. Morbidity due to asthma is not easy to measure, but hospital admission rates disclose the most severe episodes and consequently represent a relevant indicator of the burden of uncontrolled asthma in a population that has access to hospitals.

Salvador City is the capital of the State of Bahia, located in the Northeastern Region of Brazil. Its population is 2·8 million inhabitants. The proportional National Gross Product per capita estimate for Salvador is currently 2,700 US dollars. A major part of
the City population has no supplementary health insurance and is covered only by the universal public health policies.\textsuperscript{9,10} It has one of the highest prevalence rates of asthma symptoms in the Country.\textsuperscript{11} Since 2003, the Program for Control of Asthma in Bahia (ProAR), prioritizing care for patients with severe asthma, was implemented by Federal University of Bahia School of Medicine in Salvador. A preliminary prospective analysis of the first 269 subjects with severe asthma followed up for one year by ProAR central reference clinic has found a reduction of 85\% in emergency department visits, 90\% in hospitalizations and 67\% in oral corticosteroids use.\textsuperscript{12}

The objective of this study was to identify trends in asthma hospitalization rates and to evaluate the impact of ProAR in the entire City of Salvador. This was done by analysis of trends and by comparison of trends in asthma hospitalization rates before (1998-2002) and after implementation ProAR (2003-2006). The trends of asthma admissions in Salvador were compared further to those in Recife, the metropolis in Brazil most similar to Salvador; and also to trends of hospitalizations due to pneumonia and myocardial infarction in Salvador.

\section*{Methods}

\subsection*{Study design}
Analysis of routine data of the public health system on asthma hospitalizations for the entire Salvador City, before and after an intervention focused at the most severe cases of asthma. This study evaluated the impact of an intervention targeted at individuals at high risk, over the hospitalization rates of their whole community. We choose this indicator as a marked early reduction was noticed while monitoring the public health
database. We decided not to include the impact on mortality in this analysis, as the number of deaths is small and variable, validation of death certificates takes time, trends are not consistent and will require much longer observation for accurate interpretation. In a previous study of the cohort of subjects with severe asthma followed up in ProAR central reference clinic, a steep reduction in health resource utilization was detected, comprising hospitalizations and emergency visits. We did not include an evaluation of emergency visits in this study because there is no specific information on this indicator of morbidity for the entire population of Salvador in the public health database. Correspondent analysis of another city with similar characteristics was undertaken for comparison. Additional information on hospitalizations due to pneumonia and myocardial infarction in Salvador was obtained as a local control for possible variations in accessibility of health services. The number of patients enrolled in ProAR and number of those receiving inhaled corticosteroids were also taken for analysis.

Setting
ProAR is a public health intervention project supported by rules of the Brazilian Ministry of Health issued in 2002, which offered reimbursement for the costs of optimal medication to treat severe asthma. It aims to assist patients with confirmed diagnosis of severe asthma from the large underprivileged urban population that is treated in the public health system of Brazil but cannot afford the medication necessary to prevent exacerbations. Immediate priority was given to the most severe cases from Salvador, referred from emergency rooms of public hospitals throughout the City. The major role of ProAR has been to catalyze an initiative that combines contributions of all levels of public health administration (City, State and Ministry of Health) into a programme that involves health care, capacity building and research.
ProAR comprises four reference centres for specialized free medical care, pharmaceutical assistance (inhaled medication) and patient education. The education intervention was undertaken individually at the medical consultation and subsequently reinforced by the nurse and the pharmacist, as described elsewhere.\textsuperscript{15} Moreover, all patients were encouraged to attend a monthly group session with members of the ProAR professional team, including a psychologist, being offered short classes on varied topics related to asthma prevention and treatment, and plenty of time to discuss questions and concerns. We feel this is important to overcome phobias and beliefs that threaten compliance to treatment.

The reference clinics are accessible to all population and free at the point of use. A specialist checked patients referred, underwent spirometry and additional tests as required. Those with severe asthma according to GINA\textsuperscript{13} were treated with regular use of combined inhaled corticosteroid (beclomethasone or budesonide) and a long acting \(\beta_2\) agonist (formoterol) for maintenance, plus a short acting inhaled \(\beta_2\) agonist (salbutamol or fenoterol) for rescue, as needed in accordance to current international guidelines\textsuperscript{13}. Patients with persistent rhinitis received topical nasal beclomethasone concomitantly, as recommended by ARIA\textsuperscript{14}. Educational sessions for patients and family members emphasized secondary prevention and early control of exacerbations. A particular effort was placed on improving compliance to treatment, and it has resulted in a rate of objectively measured adherence of 83\%\textsuperscript{15}. From December 2002 to December 2006, 1895 patients with severe asthma entered the programme. The research projects associated with ProAR were approved by the Ethics Committee of Faculdade de Medicina da Bahia, and all subjects enrolled are asked to sign an informed consent.
Whereas the reference centres offered specialized care and free medication to patients with severe asthma, in order to build capacity for management of mild to moderate asthma, the most experienced staff of ProAR trained 512 primary health care physicians, nurses, pharmacists, social workers and managers of the public health system on prevention and management of asthma and rhinitis between 2003 and 2006. To disseminate the information of the availability of ProAR to patients with severe uncontrolled asthma, flyers containing general information, the address and telephone number of the central reference clinic were made available to all major public hospitals in the City, with special attention to emergency room staff.

**Study Population**

Data on hospitalizations were collected from all events registered in the City of Salvador. Events do not represent the number of hospitalized patients, but the number of admissions that occurred in hospitals of Salvador, among residents from this City. For comparison, we collected the same information relative to City of Recife - Northeast of Brazil. Salvador and Recife share similarities such as asthma prevalence, population ethnicity, climate, types and distribution of common allergens and socioeconomic status. Frequency of wheezing in the last year among adolescents was recently reported as 24% in Salvador and 19% in Recife\(^\text{11}\) (Table 1). Recife, like most other cities in Brazil, does not have a comparable focused asthma control program established, but several institutional and individual clinics providing care for patients with asthma of varied age groups, with no regular provision of free medication.

INSERT Table 1.
Data sources, variables and measurements

Data on hospital admissions events from each month from January 1998 to December 2006 were obtained from the national statistical database (DATASUS). DATASUS is a national database that is compulsorily filled out from standardized hospital admissions authorization forms in the whole Country. These forms are filled in by attending physicians of each hospital in Brazil in order to request payment, and confirmed by audit. Subsequently one centre only, located in Brasilia, manages the database and offers free access to the information. Other studies using this database have been published.

We decided not to include mortality data from death certificates in this analysis, as population data on cause of death is available only for earlier years. Death certificates are validated prior to their availability in the public database, and it delays the process.

The number of hospitalization events due to asthma was collected according to the place of residence of each individual (Salvador City), ICD-10, age group and gender. The number of hospitalization events was converted into hospitalization rate and analyzed separately according to gender and two age groups: < 10 years old and >10 years old. The age cut off matches the age specific criteria adopted by ProAR for case management and registries in the reference centres.

Trends in hospital admissions related to pneumonia and acute myocardium infarction in Salvador were analyzed and compared to those for asthma to evaluate the possibility of bias from the public database system and to control for any artifact caused by variation in access to hospital care. The number of units of inhaled corticosteroids and fixed
combination of corticosteroids and long acting β2 agonist bronchodilator was obtained from the pharmacies supplying medication to patients from ProAR.

Analysis of the data

The number of hospitalization events was converted into asthma hospitalization rates by dividing absolute number of events per local and year-by-year population of each city, and multiplied by 10,000 inhabitants. The procedure was done to avoid bias due to migration seasonality and variations in population numbers caused by birth and deaths in general.

Descriptive data were expressed as means and standard deviation. Linear regression modeling was performed to analyze trends and calculate differences between mean rates. The linearity equation used was $y = \beta_0 + \beta_1x$ ($y$ = hospitalization rates or in-hospital mortality rates; $x$ = calendar-year; $\beta_0$ = median rate; $\beta_1$ = median increment). Linear regression results are represented by a $R^2$ following results. Statistical significance of differences between proportions was calculated using $X^2$ Test. Correlations between hospitalization rates; mortality rates and dispensation of inhaled corticosteroids by ProAR were analyzed by using Spearman’s correlation test. Differences were considered statistically significant when $p<0.05$.

Results

Asthma hospitalizations in Salvador

18,830 events of hospitalization for asthma were registered in Salvador from 1998 to 2006. Hospitalization rates due to asthma are depicted in Table 2. The hospitalization rates declined from 12.72 to 2.25 per 10,000 inhabitants ($R^2 = 0.873$; $p<0.001$), an
82·3% reduction. The decline in hospitalizations due to asthma for the age group < 10 years old was 78·6% (R² = 0·896; p< 0·001) and for the group ≥10 years old was 93·7% (R² = 0·861; p< 0·001).

INSERT Table 2.

A greater reduction was observed from 2003 to 2006, following ProAR: 68·15 % for <10 years old and 87·5% for ≥10 years, as compared to that of the period between 1998 and 2002 (31·8% and 38·6% respectively) (p< 0·001). Hospitalization rates for acute myocardium infarction and pneumonia did not decline over the same time period (Figure 1).

Asthma hospitalizations in another city in Brazil

Recife had a reduction of 44·82% (14·87 per 10,000 inhabitants) in asthma hospitalizations from 1998 to 2006 (R²= 0·906; p<0·001). The rate of reduction in hospitalizations was greater in Salvador than in Recife: 1998-2002 (-31·76% vs. -14·45%; p < 0·001), especially after ProAR from 2003-2006 (-74·2% vs. -22·2%; p< 0·001). The rates of hospitalization due to asthma in 2006 were: 2.25/10,000 inhab. in Salvador and 17.06 in Recife.

INSERT Figure 1.

Correlation between drug dispensation and hospitalizations in Salvador

From 2003 to 2006, ProAR dispensed 220,889 units of inhaled medication for asthma control (inhaled corticosteroids and/or bronchodilators). We found a strong inverse
correlation between hospitalization rates and drug dispensation (-0.801; p <0.001) (Figure 2).

\[ \text{INSERT Figure 2.} \]

\textit{In-hospital asthma mortality}

From 1998 to 2006, 146 in-hospital deaths were related to asthma among residents of Salvador. Asthma mortality slightly increased from 19/year in 1998 to 21/year in 2002. There were 23 deaths in 2003 (0.09/10,000 inhab.) and it declined to only one in 2006. In Recife, asthma in-hospital mortality rate increased from 5/year in 2003 to 6/year in 2006.

\textbf{Discussion}

In the present study we showed a trend towards reduction in asthma hospitalizations in Salvador City from 1998 to 2006. The rate of decline seems to be enhanced after the implementation of ProAR, a government funded programme to assist patients with severe asthma of all ages. ProAR started in December 2002 and is based on the existing best evidence for case management using a multidisciplinary care approach. The decline of the asthma hospitalization rate in Salvador was greater than that observed in Recife, a similar metropolis taken for comparison. A difference of greater magnitude was encountered between Salvador and Recife during ProAR intervention (2003 to 2006) than before ProAR (1998 to 2002).

\textit{Limitations of the study}

The main possible limitation of the study would be a greater availability of hospital beds in the public health system in Recife than in Salvador, making it easier to be
hospitalized there. Indeed, the availability of beds in public hospitals in Recife was: 442/100 000 inhabitants, and in Salvador 235/100 000 in 2006.\textsuperscript{4} However, we noted that the proportional number of beds in Salvador has grown more than that of Recife from 1998 to 2006. This gives some assurance that the trends reported were not consequence of differences in access to hospitalization. On the contrary, the greater increase of availability of beds in Salvador would favour the lack of a statistical significant difference, and therefore the null hypothesis.

Seasonal influences and possible bias in the Brazilian database register were analyzed by comparison of hospitalization rates from two distinct conditions such as acute myocardial infarct and pneumonia. No consistent significant trends towards reduction in admissions due to these illnesses was found, which provides support to the hypothesis that the steeper decline observed for asthma admissions in Salvador was not related to accessibility to hospitalizations in the public health system neither to data report, and is likely a result of the intervention by ProAR. Although we did not find any clear evidence, we cannot fully exclude the possibility that certain factors exerted influence on our observations, such as general health care policies, access to health care services and asthma diagnosis and management being different between the two cities.

Reductions in hospitalization observed in Salvador may not be exclusively attributed to the ProAR intervention. Other factors could be a source of variation, such as changes in the quality and accessibility to the health services in the country, in general. In fact, the observed general trends toward reduction in admissions due to asthma in some of the Brazilian metropolis may reflect better management of asthma, in general. Nevertheless, these factors cannot explain the steeper decline in hospitalizations rates observed in
Salvador in comparison with Recife City, nor the markedly lower rate of admissions due to asthma.

The number of in-hospital deaths in Salvador is small and the marked trend towards reduction observed after the implementation of ProAR shall not be taken as conclusive. A much longer follow up is necessary for allowing definitive interpretations and will be conducted.

It would be desirable to strengthen the observations of this report with other outcomes. We are relying on hospitalizations only. However, in dealing with population outcomes in a low-resource setting, one cannot avoid taking into consideration hospital admissions as a good proxy of morbidity in diseases of low lethality. It is relevant as it indicates risk of death and cost. We have shown a steep reduction of emergency visits, of oral corticosteroids utilization, better asthma control and improved quality of life in observational studies of the ambulatory cohort of subjects with severe asthma followed up by ProAR central reference clinic.\textsuperscript{12}

**Interpretation**

Asthma hospitalizations were taken as the indicator of morbidity in this evaluation of the impact of ProAR, once it reflects the prevalence and the severity of asthma, and may predict risk of death.\textsuperscript{7,17} In the present study, asthma hospitalization rates in Salvador were compared to those observed in Recife. Both Salvador and Recife are implementing primary health care programs for their populations. Recife has active public health clinics providing asthma care, but has not developed yet a comprehensive programme focusing in severe asthma comparable to ProAR. Inhaled corticosteroids are the recommended therapy for control of persistent asthma. These medications were shown to reduce morbidity and mortality related to asthma.\textsuperscript{19,20} Ecological studies in different countries in Latin America correlate consumption of inhaled corticosteroids inversely
with asthma deaths. Various studies have shown that early and intensive patient’s education, on top of adequate treatment, is effective in reducing emergency visits and hospitalizations among enrolled subjects from low-resource settings. The novelty of the observation reported herein is the demonstration of a marked impact of a community-based intervention over hospitalizations (74% reduction) of the entire population of a city of 2.8 million inhabitants within 3 years. An intervention in Londrina (500 thousand inhab.), State of Paraná – Brazil, aiming at building capacity of primary health care workforce and strengthening the health system for asthma control, as opposed to our prioritization of the control of the most severe cases, has recently demonstrated a 32% reduction in asthma hospitalizations in a similar time frame. In Finland, a high-income country of 5.3 million inhabitants, a 54% reduction in hospitalizations over 10 years was shown after their asthma programme was implemented. To our knowledge, we report on the first demonstration of a rapid and dramatic impact of a targeted public health intervention for control of asthma in a large city of a developing country.

A study comparing patients with severe asthma one year before and one year after admission to ProAR reported a reduction in emergency visits and hospitalizations over 80%. The present study is based on a public health database from which the number of hospital admissions by cause and city of residence is obtained. Due to confidentiality precautions, it is not possible to know which of the patients hospitalized attended our intervention program. In the future, while looking at asthma mortality and hospitalizations trends, we intend to ask for a special authorization to perform linkage analysis combining the database of ProAR patients and the Brazilian public health database (DATASUS). The precise number of severe asthmatics in Salvador is unknown. However, projecting the preliminary results to the whole of the population assisted by ProAR, and considering it might avoid one hospital admission for each patient/year, over 1,000 hospitalizations could be prevented every year. Indeed, moving from preliminary estimates to data analysis we noted that 1,619 hospitalizations due to
asthma have been averted in the City of Salvador in the last year analyzed (2006). ProAR may have matched the hypothetical expectations, well over the already declining trends.

The reduction of hospitalizations in Salvador was not clear from 2003 to 2004, but only in 2005 and 2006. The explanation to this progressive effect, resembling a dose-response curve, is the cumulative enrollment of patients with severe asthma, as presented in Figure 2, which took place over the years.

The data presented here reiterate the current knowledge that the more patients with asthma have access to inhaled corticosteroids the less likely they are to be hospitalized for asthma, and adds evidence on an efficient strategic prioritization for community interventions for control of asthma that may be extremely useful in communities of limited resources.

The intervention for control of asthma implemented by ProAR comprises a multifaceted approach including several inter-related crucial steps: screening of referrals for asthma severity, differential diagnosis and investigation of co-morbidities, treatment planning, pharmaceutical assistance and education, all of them previously proven to be important for case management. In this study we assessed the whole of the approach and we cannot draw any inference from the role of individual components.

The high proportion of adherence to the treatment we have reported in ProAR\textsuperscript{15} certainly contributes to the favourable results. It was made possible by the provision of medications for free. It would be very difficult to obtain a comparable rate of compliance within this low-resource setting had the patients needed to pay for their care
or their medication.

Some studies have raised concerns regarding the long-term safety of long acting beta 2 agonist bronchodilators, which might be associated with risk of hospital admissions and deaths.\textsuperscript{21,22,23} Our results indicate that any potential risk of hospitalizations has been largely surpassed by the benefit of our approach to management of severe asthma, including the use of combined long acting beta 2 agonist and inhaled corticosteroids as recommended by current guidelines.

\textit{Generalizability}

Asthma, a global health problem, causes relevant morbidity, numerous deaths and high costs to the families and to the health systems.\textsuperscript{1,2} The costs of asthma are related to severity of disease\textsuperscript{1}, and hospitalizations represent 50\% of all the expenditures with asthma.\textsuperscript{24,25} A study of cost-effectiveness performed to evaluate ProAR showed that the intervention resulted in incremental economy to patients, their families, and the health system.\textsuperscript{26}

Although asthma hospitalizations have decreased in recent years in Brazil, in large urban centres such as Recife and Salvador, they seem to decrease slowly since 1998 as showed in Table 2. In Salvador, the implementation of ProAR in 2003 has likely accelerated these declining trends. In the present study the number of inhaled medications dispensed for asthma control was inversely correlated with hospitalization rates.
The most important novel observation of this study is the rapid reduction in asthma admissions in a City of 2·8 million inhabitants, after a very focused intervention targeting patients at greater risk. This observation needs to be reproduced in other locations, as it would be of remarkable importance to public health in countries with high morbidity due to asthma and limited resources. We speculate that the most important factors that determined our favourable results were: 1) considerable proportion of patients with severe asthma with no access to good quality care including affordable medication at baseline; 2) establishment of treatment with the most effective and safe medications; 3) education program to increase compliance to proper medication use; 4) referral system made easy to patients and health services. Given these four conditions, it seems unlikely that a similar intervention may fail.

**Conclusion**

A public health intervention for asthma control targeted at the most severe cases, providing free health care and medication, was associated with a rapid reduction in asthma hospital admissions in Salvador, Brazil.

**Word count:** 3776

**Contributors**

Carolina Souza-Machado designed the study, collected data, analyzed data, interpreted results and wrote a draft of the paper.

Adelmir Souza-Machado is co-mentor of this study, supervised fieldwork and analysis, interpreted results and edited the paper.
Rosana A. Franco, Eduardo V. Ponte and Jean Bousquet interpreted results and edited the paper.

Alvaro A Cruz proposed and designed the study, supervised the analysis of results, interpreted results and edited the paper.

Laura Rodrigues suggested the study question and data analysis, contributed to interpretation of results and edited the paper.

Mauricio L Barreto contributed to the study design, data analysis and interpretation of the results and edited the paper.

**Conflict of Interest**

The authors declare no conflict of interest in relation to this study.

**Acknowledgements**

The authors thank all staff of ProAR, for their technical assistance, especially Ms Ana Tereza Campos, the administrator; Daniela Ramos and Daisy Naiane F. Silva (undergraduate students) for their important support.
References


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Figure 1. Hospitalization rates due to asthma, pneumonia and acute myocardial infarction (AMI) in Salvador and Recife – Brazil, from 2002 to 2006. The arrow indicates the year the Programme for Control of Asthma in Bahia (ProAR) implementation started.
Figure 2. Asthma hospitalization rates, number of patients enrolled in the Programme for Control of Asthma in Bahia (ProAR) and number of dispensed units of medication containing inhaled corticosteroids (ICS), as a single medicine or in combination (per 1000) in Salvador – Brazil, from 2002 to 2006.
Table 1. Characteristics of the population of the cities of Salvador and Recife, Brazil.

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<tr>
<th>Features</th>
<th>Salvador</th>
<th>Recife</th>
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<tr>
<td>Proportion of females</td>
<td>52.9%</td>
<td>53.5%</td>
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<td>Proportion &gt; 10 yrs (%)</td>
<td>83.0%</td>
<td>83.2%</td>
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<tr>
<td>Prevalence of wheezing in the last 12 months among adolescents 11</td>
<td>24.6%</td>
<td>19.1%</td>
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Table 2. Asthma hospitalization rates per 10,000 inhabitants in Salvador and Recife cities from 1998 to 2006.

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<tbody>
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<td><strong>Salvador</strong></td>
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<tr>
<td>Frequency of hospitalizations</td>
<td>2,894</td>
<td>3,233</td>
<td>2,659</td>
<td>1,972</td>
<td>2,188</td>
<td>2,230</td>
<td>2,016</td>
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<td>611</td>
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<td>-1619</td>
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<tr>
<td>Hospitalization rate (/10,000 inhab.)</td>
<td>12.72</td>
<td>14.04</td>
<td>10.88</td>
<td>7.93</td>
<td>8.68</td>
<td>8.72</td>
<td>7.77</td>
<td>3.84</td>
<td>2.25</td>
<td>-4.04 (-31.76%)</td>
<td>-6.47** (-74.2%)</td>
<td>-10.47</td>
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<tr>
<td><strong>Recife</strong></td>
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<tr>
<td>Hospitalization rate (/10,000 inhab.)</td>
<td>30.92</td>
<td>30.13</td>
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<td>17.06</td>
<td>-4.47 (-14.45%)</td>
<td>-4.87** (-22.20%)</td>
<td>-13.86</td>
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\*\(^p<0.001\) for general comparison of variation between Salvador and Recife Cities.

\**\(^p<0.001\) for comparison between \(\Delta 1\) and \(\Delta 2\) in Salvador and Recife.

1\(^\text{st}\) Variation of hospitalization from 1998 to 2002 (absolute and percentual).

2\(^\text{nd}\) Variation of hospitalization from 2003 to 2006 (absolute and percentual).

3\(^\text{rd}\) General variation of hospitalization from 1998 to 2006 (absolute and percentual).