Evolution of acute lower respiratory infection in children aged < 5 years in Morocco from 2005 to 2014

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Abstract

Background: Acute lower respiratory infection is a major cause of death in children aged < 5 years in Morocco. The 13-valent pneumococcal conjugate vaccine (PCV) was introduced to the Moroccan National Immunization Programme in 2010.

Aims: To investigate the trend in the incidence of acute lower respiratory infection in children aged < 5 years during 2005–2014 in Morocco.

Methods: Data on acute lower respiratory infection in children aged < 5 years were obtained from the data published annually by the Moroccan Ministry of Health. We used joinpoint regression analysis to estimate the trend in incidence of acute lower respiratory infection during the study period.

Results: The incidence of acute lower respiratory infection increased significantly between 2005 and 2011: by 3.08% annually in children aged < 5 years and by 3.24% annually in children aged 1 to < 5 years. However, the incidence was stable after 2011 as the observed trends were not significant, although the incidence decreased from 2011 to 2014 by 4.26% annually in children aged < 5 years, by 3.57% annually in children aged 1 to < 5 years and by 5.14% annually in urban areas.

Conclusions: Our results suggest a probable influence of the PCV on the trend in incidence of acute lower respiratory infection in Morocco.

Keywords: acute lower respiratory infection, pneumococcal conjugate vaccine, children, joinpoint regression, Morocco

Introduction

Acute lower respiratory infections (ALRIs), such as pneumonia and bronchiolitis, are the leading cause of morbidity and mortality in children aged < 5 years. According to recent estimates, every year about 120–156 million cases of ALRI occur globally, with ~1.4 million resulting in death. More than 95% of these deaths occur in low- and middle-income countries (1–3).

ALRI is caused by a number of infective agents, with *Streptococcus pneumoniae* being the most frequently identified bacterium and respiratory syncytial virus the most common virus (4). *S. pneumoniae* is responsible for a large proportion of the morbidity and mortality burden worldwide (1). It causes a wide range of diseases, from acute upper respiratory tract infections to severe invasive infections such as meningitis and severe pneumonia (1). The Institute for Health Metrics and Evaluation estimated that *pneumococcus* was responsible for 393 000 pneumonia deaths in children younger than 5 years in 2015 (2), and it is the leading cause of bacterial pneumonia, with an estimated 335 000 deaths in 2015 (3).

The pneumococcal conjugate vaccine (PCV) was introduced in the United States of America (USA) in 2000, and covered the 7 pneumococcal serotypes circulating in the USA (4, 6B, 9V, 14, 18C, 19F and 23F). The National Vaccination Program with 7-valent PCV resulted in a marked decrease in the incidence of severe pneumonia and a reduction in hospital mortality from severe pneumonia (4). PCV has also reduced the incidence of pneumonia in unvaccinated populations by reducing colonization of the nasopharynx in vaccinated children (4), and through herd immunity (5,6). Other studies have also shown a reduction in invasive pneumococcal diseases after introduction of PCV (7,8).

In Morocco, ALRI is a major cause of death in children aged < 5 years (9). In view of the importance of these infections, Morocco set up a national programme in 1993 to control acute respiratory infections in children. In 1997, the Moroccan Ministry of Health began progressively implementing the World Health Organization's Integrated Management of Childhood Illness (IMCI) strategy. The strategy promotes the use among health workers of evidence-based clinical guidelines in outpatient settings by using standardized clinical case definitions to identify and treat common causes of childhood death. In first-level health facilities, the clinical case definition of pneumonia, which is the main cause of ALRI, is based on

2 simple clinical endpoints: fast breathing and drawing in of the lower chest wall (*10*). The PCV was introduced in the Moroccan National Immunization Programme in 2010 (*9*); the 13-valent PCV was introduced in October 2010 and was replaced by 10-valent PCV in July 2012 (*11,12*). The vaccination consists of 3 injections: the first at 2 months, the second at 4 months and the third at 12 months. PCV coverage was 15% in 2010, 23% in 2011 and reached 70–80% from 2012 (data from the Moroccan Ministry of Health).

The aim of the present study was to investigate the trend in incidence of ALRI in children aged < 5 years between 2005 and 2014 in Morocco.

Methods

Study design and population

This study was conducted in Morocco, situated in the northwest of Africa. We considered the administrative division of Morocco into 16 regions (*13*), as the study concerned the period before the divisional change in 2015 (*14*). The estimated population of Morocco in 2014 was around 34 million (*15*), with a life expectancy at birth of 74.8 years (*16*). About 10% of the population was aged < 5 years (*15*). The fertility rate in 2014 was 2.21 births per woman (*15*).

We conducted a retrospective observational study using data provided by the national programme for controlling acute respiratory infections in children and published annually by the Moroccan Ministry of Health (*16*). The definition of ALRI was based only on clinical criteria. Cases were mainly reported from public hospitals and public health centres. Private health facilities do not participate much in the surveillance system. All levels of severity of ALRI were reported but unfortunately, we did not have data stratified by stage of severity.

Data on ALRI in children aged < 5 years from 2005 to 2014, as well as the target populations during these years, were collected from the data published annually by the Moroccan Ministry of Health (*16*). Data on the number of ALRI cases and the target population were collected by region, age group (< 1 year and 1 to < 5 years) and residence (urban and rural).

Statistical analysis

The trend in ALRI incidence was assessed by regression analysis using Joinpoint Regression Program, version 4.2.0.2. The incidence of ALRI was calculated as the number of reported cases divided by the target population by region according to age group (< 1 year or 1 to < 5 years) and residence (urban or rural). Multiple reports for the same child in the same year were removed by the data provider so that a case was counted only once.

The Joinpoint Regression Program is a statistical software package that computes and analyses nonlinear, piecewise trends of time series. The trend is computed in segments that are connected together at joinpoints. If there are no joinpoints, the trend is flat and displayed as a straight line. Joinpoint uses a Monte Carlo permutation test to detect years when significant changes in rate trends occur (*17*). The joinpoint regression is different from other similar models, like piecewise regression, because it has the constraint of continuity at the change points, and the choice of the number of joinpoints and their locations is estimated within the model. A distinguishing characteristic of this model is that the minimum and maximum number of joinpoints allowed is arbitrarily set before the analysis, while the final number of joinpoints is not fixed *a priori* by the researcher, as in a classical piecewise regression model, but it is established on the basis of a statistical criterion.

The software calculates the annual percentage change (APC) and its 95% confidence interval (CI) for each trend segment. APC is 1 way to characterize trends in incidence rates over time. When the Log Transformation option on the Input File tab is ln(y) = xb, then the output calculates the estimated APC. With this approach, the incidence rates are assumed to change at a constant percentage of the rate of the previous year (*17*). For example, if the APC is 1%, and the rate was 50 per 100 000 in 1990, the rate was 50 – 1.01 = 50.5 in 1991 and 50.5 – 1.01 = 51.005 in 1992. Rates that change at a constant percentage every year change linearly on a log scale. For this reason, to estimate the APC for a series of data, the following regression model is used (*17*):

$$\log(R_y) = b_0 + b_1 y \text{ where } \log(R_y) \text{ is the natural log of the rate in year } y.$$

$$\text{The APC from year } y \text{ to year } y + 1 = \left[\frac{R_{y+1} - R_y}{R_y}\right] \times 100$$

$$= \frac{\{e^{b_0 + b_1(y+1)} - e^{b_0 + b_1(y)}\}}{e^{b_0 + b_1(y)}} \times 100$$

$$= (e^{b_1} - 1) \times 100$$

It is not always reasonable to expect that a single APC can accurately characterize the trend over an entire series of data. The joinpoint model uses statistical criteria to determine when and how often the APC changes. For incidence rates, it is fit using joined log-linear segments, so each segment can be characterized using an APC. For example, incidence rates may rise gradually (positive APC) for a period of several years, rise sharply for several years after that, and then drop gradually (negative APC) for the next several years. Finding the joinpoint model that best fits the data allows us to determine how long the APC remained constant and when it changed (*17*).

For any segment with slope β, the APC is 100 {exp(β) – 1}. The 100(1 – α)% confidence limits are (*17*):

$$Lower = 100\{exp(\beta - s^* t_d^{-1}(1 - \alpha/2)) - 1\}$$
$$Upper = 100\{exp(\beta + s^* t_d^{-1}(1 - \alpha/2)) - 1\}$$

where d is the degrees of freedom and s is the standard error for the slope and $t_d^{-1}(q)$ is the qth quantile of a t distribution with d degrees of freedom. The P value for a 2-sided test for which the true APC is 0 is calculated based on a t distribution.

The analysis was performed for all children aged < 5 years, followed by a stratified analysis by age group,

residence area and region. We did not perform a sex-specific analysis or other specific analyses because the data published in the Ministry of Health report only included age group. The APCs before and after the joinpoint for the different regions were represented using the Linked Micromaps software.

Ethical approval and consent to participate

This study was approved by the Ethics Committee of the Faculty of Medicine and Pharmacy, Mohamed V University, Rabat. All data are presented in aggregate form without any individual identification in the report of the Ministry of Health of Morocco, which is openly available on the Ministry of Health website (16).

Results

During 2005–2014, 2 338 282 cases of ALRI occurred in Morocco (Table 1). Most cases were children aged 1 to < 5 years (1 545 357, 66.1%) and occurred in urban areas (1 401 437, 60.0%).

The incidence of ALRI increased significantly between 2005 and 2011: by 3.08% in children aged < 5 years (APC = 3.08, 95% CI: 0.7–5.6) (Figure 1), by 3.24% in children aged 1 to < 5 years (APC = 3.24, 95% CI: 0.6–6.0)

Table 1 **Distribution of cases of ALRI in children in Morocco by age group, residence and region 2005–2014**

Variable	No. (%)
ALRI in children aged < 5 years	2 338 282 (100.0)
Age group (years)	
0–1	792 925 (33.9)
1 to < 5	1 545 357 (66.1)
Residence	
Urban	1 401 437 (59.9)
Rural	936 845 (40.1)
Region	
Tanger-Tetouan	265 431 (11.4)
Gharb-Chrarda-Beni Hssen	131 207 (05.6)
Taza-Al Hoceima-Taounate	101 525 (04.3)
Oriental	128 073 (05.5)
Rabat-Sale-Zemmour-Zaer	266 172 (11.4)
Grand Casablanca	331 676 (14.2)
Fes-Boulemane	119 871 (05.1)
Chaouia-Ourdigha	118 893 (05.1)
Doukala-Abda	679 19 (02.9)
Marrakech-Tensifet-Al Haouz	304 806 (13.0)
Tadla-Azilal	906 94 (03.9)
Sous-Massa-Draa	213 929 (09.1)
Meknes-Tafilalet	141 039 (06.0)
Guelmim-Es Semara	359 50 (01.5)
Laayoune-Boujdour-Sakia El Hamra	145 53 (00.6)
Oued Ed Dahab-Lagouira	6 544 (00.3)

ALRI = acute lower respiratory infection.

Figure 1 **Trend in the incidence of acute lower respiratory infections in children <5 years, Morocco, 2005–2014.**
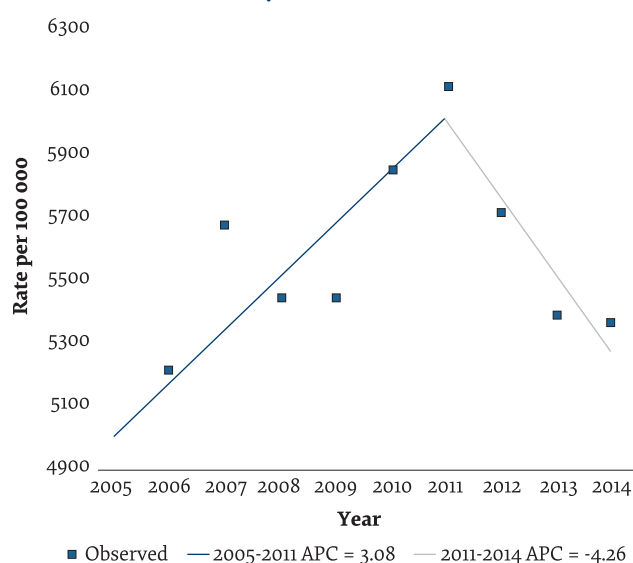
APC = annual percentage change.

and by 4.27% in urban areas (APC = 4.27, 95% CI: 1.3–7.6) (Figure 2A). However, the incidence was relatively stable after 2011 as the observed trends were not statistically significant, although the incidence decreased from 2011 to 2014 by 4.26% in children aged < 5 years (APC = –4.26, 95% CI: –10.9 to 2.8) (Figure 1), by 3.57% in children aged 1 to < 5 years (APC = –3.57, 95% CI: –10.7 to 4.1) and by 5.41% in urban areas (APC = –5.41, 95% CI: –13.6 to 3.3) (Figure 2A). The joinpoints corresponded to the year 2011 (95% CI: 2007–2012) for children aged < 5 years, children aged 1 to < 5 years and in urban areas (Table 2).

The incidence of ALRI increased from 2005 to 2011: by 2.17% in children aged < 1 year (APC = 2.17, 95% CI: –0.2 to 4.5) and by 0.99% in rural residence (APC = 0.99, 95% CI: –1.4 to 3.4) (Figure 2B) but these increases were not significant. The incidence decreased from 2011 to 2014: by 5.60% in children aged < 1 year (APC = –5.60, 95% CI: –11.7 to 1.0) and by 2.82% in rural residence (APC = –2.82, 95% CI: –9.3 to 4.3) (Figure 2B) but these decreases were also not significant. The joinpoints corresponded to the year 2011 (95% CI: 2007–2012) for children aged < 1 year and in rural residence (Table 2).

In 8 out of 16 regions, there was an increase in the incidence of ALRI before the joinpoint, a significant increase in 3 of them, and a decrease in the incidence after this joinpoint in 12 of 16 regions, a significant decrease in 1 of them (Figure 3, Table 2). The 95% CI of these 8 joinpoints included the period following PVC introduction (Table 2).

Discussion

Our results showed a break in the trend of increasing incidence of ALRI in children aged < 5 years in 2011 (1 year after introduction of the PCV in the national immunization programme in Morocco). The incidence increased significantly before the joinponit (positive APC) and

Figure 2 Trend in the incidence of acute lower respiratory infections in children <5 years by residence, Morocco, 2005–2014: (A) urban residence, (B) rural residence
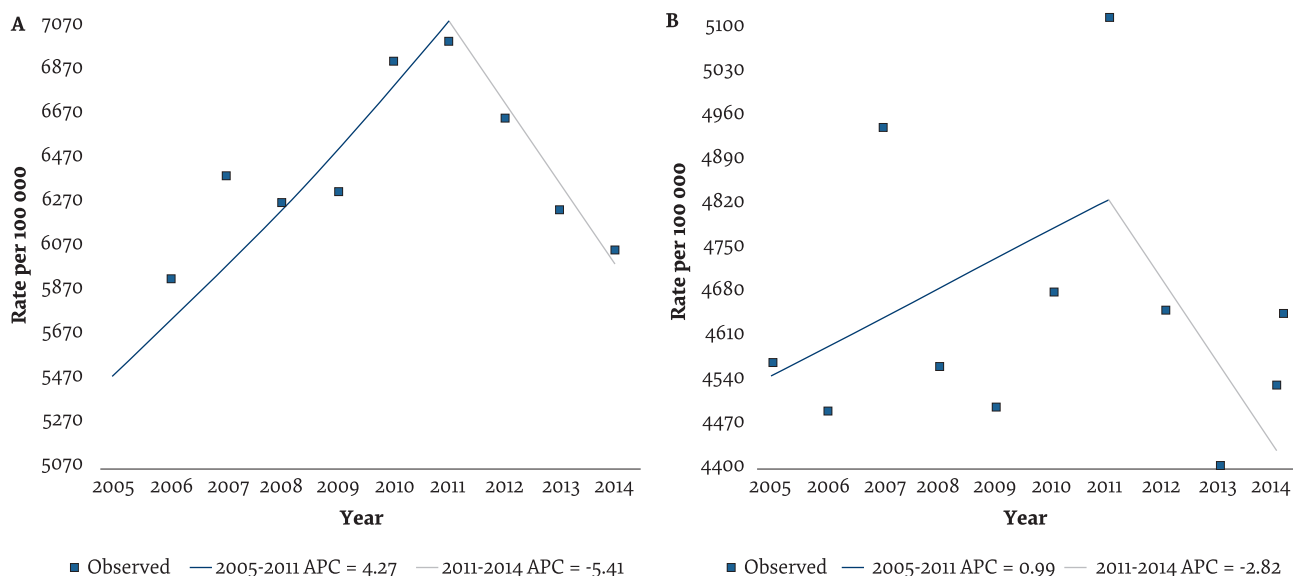
APC = annual percentage change.

decreased after the joinpoint (negative APC). This decrease could have been due to multiple factors such as a training programme for diagnosis of ALRI, or changes in health system practices. We hypothesize that this de-

crease could also be explained by the introduction in 2010 of the PCV in the national immunization programme in Morocco. We observed a significant decreasing trend or stabilization in incidence of ALRI, in children aged 1 to <

Table 2 APC in acute lower respiratory infection before and after joinpoints by age, residence and region in Morocco, 2005–2014

Variable	APC before joinpoint	APC after joinpoint	Joinpoint	95% CI
Children aged <5 years	3.08[a]	-4.26	2011	2007–2012
Age group (years)				
0–1	2.17	-5.60	2011	2009–2012
1 to < 5	3.24[a]	-3.57	2011	2007–2012
Residence				
Urban	4.27[a]	-5.41	2011	2007–2012
Rural	0.99	-2.82	2011	2007–2012
Region				
Tanger-Tetouan	13.20	-0.71	2007	2007–2012
Gharb-Chrarda-Beni Hssen	3.32	-4.45[a]	2007	2007–2012
Taza-Al Hoceima-Taounate	6.39	-13.54	2012	2007–2012
Oriental	0.64	-4.02	2011	2007–2012
Rabat-Sale-Zemmour-Zaer	20.66[a]	1.80[a]	2007	2007–2008
Grand Casablanca	28.84[a]	-1.15	2008	2007–2012
Fes-Boulemane	6.36[a]	-13.53	2012	2008–2012
Chaouia-Ourdigha	-1.87	-10.96	2011	2007–2012
Doukala-Abda	-6.72	0.67	2009	2007–2012
Marrakech-Tensifet-Al Haouz	1.40	-1.73	2012	2007–2012
Tadla-Azilal	24.75	-3.20	2007	2007–2009
Sous-Massa-Draa	-0.39	-8.43	2011	2008–2012
Meknes-Tafilalet	1.86	-6.91	2011	2007–2012
Guelmim-Es Semara	-7.30[a]	17.35	2011	2008–2012
Laayoune-Boujdour-Sakia El Hamra	-16.59[a]	27.57[a]	2010	2009–2012
Oued Ed Dahab-Lagouira	13.49[a]	-6.59	2010	2007–2012

[a]*Annual percentage change is statistically different from 0 at = 0.05.*
APC = annual percentage change; CI = confidence interval.

Figure 3 Annual percentage change (APC) before and after joinpoints by region, Morocco, 2005–2014.
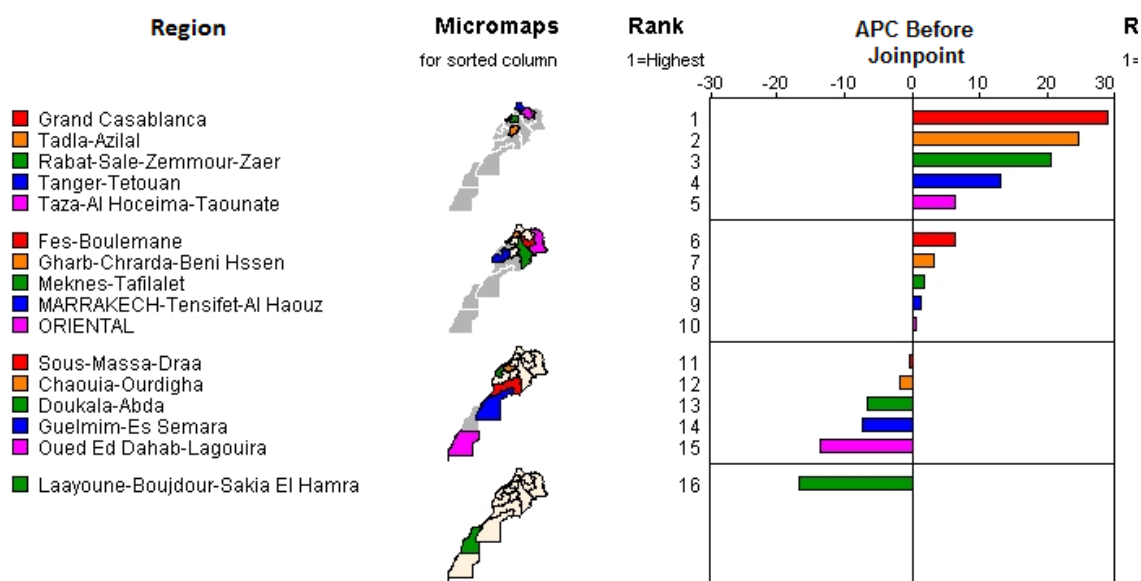
5 years, in urban areas, and in 3 of 16 regions, which were among the most populated. The 95% CI of joinpoints included the postvaccination period. This suggests efficacy of the PCV in preventing ALRI. The difference in trend was more evident in urban than rural areas and children aged 1 to < 5 years compared with < 1 year because the number of cases was more important in these 2 groups, so the power was sufficient to show a significant difference.

Several studies have highlighted the effect of introduction of PCV in reducing respiratory infections (18–21). Furthermore, randomized clinical trials have shown that PCV prevents pneumonia (22–24). However, efficacy estimates have varied according to the case definition of pneumonia. Vaccine efficacy against clinically diagnosed pneumonia was 6% for 7-valent PCV in the Northern California Kaiser Permanente trial (22) and 7% for a 9-valent PCV in a Gambian trial (23). A trial in South Africa also using a 9-valent PCV reported efficacy of 16% for pneumonia admissions (24). Vaccine efficacy estimates were consistently higher when radiological confirmation was included as part of the case definition – 18% in the Kaiser Permanente trial (22), 17% in the South African trial (24) and 37% in the Gambian trial (23).

There were some limitations to our study. (1) The decrease in incidence 1 year after PCV was introduced was not significant, except in Gharb-Chrarda-Beni Hssen. This could have been due to lower statistical power because of limited time (only 3 years) after the joinpoint. (2) The analytical method used was exploratory and did not take into account any other factors that may influence the trend in the incidence of ALRI; in particular, the level of regional implementation of the programme to control ALRI in children. Further analysis, including interrupted time series analysis with a multivariate approach, could be used to answer this question more thoroughly. (3) The surveillance system in Morocco is managed exclusively by the Ministry of Health and it is mostly based on

the public sector. While its representativeness could be questioned, the trends shown by the data collected are not biased because there was no change in the surveillance organization during the study period (4). Cases of ALRI are based on passive surveillance data and this may result in under-reporting. However, this bias would have a small effect on our results since under-reporting would persist over time (5). The definition of ALRI was based only on clinical criteria, we did not have information about the causative agents, and ALRI can be caused by bacteria and viruses other than *S. pneumoniae* (6). The calculated incidence was biased because cases counted in the numerator corresponded to those notified only in the public sector (7). We did not include a control group for assessing our results (8). In Guelmim-Essemara, Laayoune-Boujdour-Sakia El Hamra and Oued Ed Dahab-Lagouira, there was a significant decreasing trend in the incidence of ALRI before the joinpoint of PCV introduction and this was stable after the joinpoint, except for Laayoune-Boujdour-Sakia El Hamra. The CI of the joinpoint includes the postvaccination period. These southern regions are desert areas and are less populated. This observation may be also due to an increase in the number of reports following awareness campaigns or other factors favouring a rise in ALRI cases, especially a decline in breastfeeding in these regions.

In spite of these limitations, our study is important because it is the first national study in Morocco to assess the effect of PCV introduction on the trend in the incidence of ALRI, using national epidemiological surveillance data.

Conclusion

Our results suggest that PCV has influenced the trends in incidence of ALRI in Morocco. However, the analytical method used cannot provide strong evidence about this relationship and this hypothesis must be explored by further studies.

Mesure de l'évolution de l'infection aiguë respiratoire basse chez l'enfant de moins de cinq ans au Maroc de 2005 à 2014

Résumé

Contexte : L'infection aiguë respiratoire basse constitue une cause majeure de décès chez les enfants de moins cinq ans au Maroc. Le vaccin antipneumococcique conjugué 13-valent (VPC 13) a été introduit dans le cadre du Programme de vaccination national du Maroc en 2010.

Objectifs : Mesurer l'évolution de l'incidence de l'infection aiguë respiratoire basse chez les enfants de moins de cinq ans durant la période comprise entre 2005 et 2014 au Maroc.

Méthodes : Des données sur l'infection aiguë respiratoire basse chez les enfants de moins de cinq ans ont été obtenues à partir des données publiées chaque année par le ministère de la Santé marocain. Nous avons recouru à l'analyse de régression joinpoint pour estimer la tendance de l'incidence de ce type d'infections pendant la période de l'étude.

Résultats : L'incidence de l'infection aiguë respiratoire basse a augmenté de manière significative entre 2005 et 2011 de 3,08 % par an chez les enfants de moins de cinq ans et de 3,24 % par an chez les enfants dont l'âge était compris entre un et moins de cinq ans. Cependant, l'incidence était stable après 2011, les tendances observées n'étant pas significatives, bien que l'incidence ait diminué de 4,26 % par an entre 2011 et 2014 chez les enfants de moins de cinq ans, de 3,57 % par an chez les enfants dont l'âge était compris entre un et moins de cinq ans et de 5,14 % par an dans les zones urbaines.

Conclusions : Nos résultats suggèrent une influence probable du VPC 13 sur l'évolution de l'incidence de l'infection aiguë respiratoire basse au Maroc.

تطور عدوى الجهاز التنفسي السفلي الحادة في الأطفال الذين تقل أعمارهم عن 5 سنوات في المغرب في الفترة بين عامي 2005 و2014

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الخلاصة:

الخلفية: تُعتبر عدوى الجهاز التنفسي السفلي الحادة أحد الأسباب الرئيسية للوفاة في الأطفال الذين تقل أعمارهم عن 5 سنوات في المغرب. وأُدخل اللقاح المتقارن المضاد للمكونات الرئوية المكوّن من 13 عنصراً في البرنامج الوطني للتحصين في المغرب في عام 2010.

الأهداف: هدفت هذه الدراسة إلى تحري الاتجاه السائد في معدل الإصابة بعدوى الجهاز التنفسي السفلي الحادة في الأطفال الذين تقل أعمارهم عن 5 سنوات في الفترة 2005–2014 في المغرب.

طرق البحث: تم الحصول على بيانات عن الإصابة بعدوى الجهاز التنفسي السفلي الحادة في الأطفال الذين تقل أعمارهم عن 5 سنوات من البيانات التي تُنشرها سنوياً وزارة الصحة المغربية. وقد استخدمنا تحليل انحدار النقط لتقدير الاتجاه السائد في معدل الإصابة بعدوى الجهاز التنفسي السفلي الحادة خلال فترة الدراسة.

النتائج: ارتفع معدل الإصابة بعدوى الجهاز التنفسي السفلي الحادة ارتفاعاً كبيراً في الفترة بين عامي 2005 و2011: بنسبة 3.08٪ سنوياً في الأطفال الذين تقل أعمارهم عن 5 سنوات، وبنسبة 3.24٪ سنوياً في الأطفال الذين تتراوح أعمارهم بين سنة إلى أقل من 5 سنوات. وعلى الرغم من ذلك، كان معدل الإصابة ثابتاً بعد عام 2011، إذ أن الاتجاهات الملحوظة لم تكن ذات أهمية، على الرغم من زيادة معدلات الإصابة من عام 2011 إلى عام 2014 بنسبة 4.26٪ سنوياً في الأطفال الذين تقل أعمارهم عن 5 سنوات، وبنسبة 3.75٪ سنوياً في الأطفال الذين تتراوح أعمارهم بين سنة إلى أقل من 5 سنوات، وبنسبة 5.14٪ سنوياً في المناطق الحضرية.

الاستنتاجات: تُشير نتائجنا إلى تأثير محتمل للقاح المتقارن المضاد للمكونات الرئوية على اتجاه معدل الإصابة بعدوى الجهاز التنفسي السفلي الحادة في المغرب.

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