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ARTICLE

Trends and health burden of hospitalized acute respiratory infections and impact of Haemophilus influenza immunization in a Tunisian university hospital: a twelve-year study

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ABSTRACT

Background: We aimed to describe the episodes and trends of admissions for community-acquired Respiratory Infections (RI) over a 12-year period and to assess the impact of Haemophilus influenza type b (Hib) vaccine on RI admissions in children aged up to 3 years.
Methods: We conducted a twelve-year retrospective observational study on all community-acquired RI admitted to Fattouma Bourguiba Hospital in Monastir Governorate (Tunisia) from 1 January 2002 to 31 December 2013. RI cases were selected from the Regional Registry of Hospital Morbidity. Data were coded according to ICD-10. To assess the impact of the Hib vaccine, three cohorts were defined based on vaccine status (unvaccinated cohort, first vaccinated cohort (VC) by monovalent form and second VC by pentavalent combination).
Results: Admissions for RI represented 17.6% (CI95%: 17.3–18.1) of all communicable diseases hospitalizations (n = 6 061/34 289). The crude incidence rates (CIR) per 100,000 inh were 24.2 for upper RI (URI) and 77.5 and for Lower RI (LRI) (p < 0.0001). Pneumonias represented 53.9% of LRI. Sex-ratio (male/female) was 1.12 for URI and 1.64 for LRI (p < 0.0001). At admission, the median age was 22 years (IQR: 3–52). Admission for Pneumonia increased significantly during study period (slope 'b' = 5.16; p < 0.0001) especially in children up to 5 years old (slope 'b' = 5.53) and in elderly (slope 'b' = 2.13). Among children up to 3 years old, the CIRs per 100,000 for Hib pneumonia admission were 11.6 in Non-Vaccinated Cohort (NVC), 10.6 in Vaccinated Cohort (VC) by protocol 1 (Hib Vaccine monovalent) and 0.80 in VC by protocol 2 (pentavalent vaccine combination).The relative risk reduction was 99% for protocol 2 (p < 0.001).
Conclusion: Admissions for RI in a tertiary level hospital were common with an increasing trend. The Hib immunization program, in particular the pentavalent combination, has had a positive impact on the reduction of related acute diseases.

1. Introduction

Community-acquired Respiratory Infections (RI) is a frequent, severe and costly public health problem. RIs are particularly common in the two extreme age groups (children and the elderly) because of their fragility and comorbidities [1]. RI admission criteria in university hospital are related to the severity of clinical and radiological signs. Trends of RI had an important fluctuation over time. In last decades the decrease of communicable diseases was spectacular. Several factors, however, have reversed these trends, including increased resistance to antibiotics, irregular vaccination programs and drastic climatic changes [2]. In 2015, upper respiratory infections (URI) had globally acute incidence in excess of 1 billion (17.2 billion, 95%

CI: 15.4–19.2 billion) [3]. Lower respiratory infections (LRI) are a major cause of morbidity and mortality worldwide especially among children under 5 years (1.4 million deaths) [4,5]. Community-acquired pneumonia (CAP) represents 5% to 12% of all adult LRI managed in general practice [6]. *Streptococcus pneumonia* (SP) and *Haemophilus influenza* type b (Hib) are the main pathogens that caused RI [7,8]. Many efforts are ongoing worldwide to improve awareness of health-care professionals about antibiotic resistance and to standardize vaccination programs [9].

In Tunisia, few studies have focused on the epidemiology of RI and evaluated the impact of the strategies followed by health professionals to manage this public health problem. The Tunisian Expanded Program of Immunization (TEPI) was introduced in 1979 targeting

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world common bacterial diseases. As for vaccines for respiratory diseases in this program, Hib vaccine was provided as liquid Hib conjugate vaccine (monovalent) between 2002 and 2005 and then reintroduced in 2011 as Hib conjugate in combination with Hepatitis B, diphtheria, Poliomyelitis and Tetanus (DPT) called the pentavalent vaccine [10]. Currently, the TEPI includes the Hib vaccine and the pneumococcal vaccine. The latter has just been included in April 2019.

This study aimed to describe the frequency, trends and health burden of admissions for RI during a period of 12 years in a low-middle income country. We sought also to assess the impact of both forms of Hib vaccine on admissions among hospitalized children aged up to 3 years.

2. Methods

2.1. Study design

We carried out a twelve-year retrospective observational study using the regional register morbidity data of hospitalized people in a university hospital in Tunisia.

3. Study *setting*

Monastir is a coastal city in Tunisia. The population of Monastir represented 4.99% of the Tunisian population. This study was conducted in the main university hospital of this city. According to the Tunisian health card 2015, the total capacity of beds in public and private hospital structures in Monastir was in total 1441 beds of which 82% belonged to the public sectors. University Hospital Fattouma Bourguiba is the unique third line hospital in the region of Monastir and it has a capacity of 858 beds (73% of total public beds) and a workforce of 248 doctors and pharmacists [11]. It included 1177 health professionals. Emergency, Pediatric, Pulmonary, Otorhinolaryngology and Infectious departments managed the quasi totality of community-acquired RI cases.

3.1. Participants

We included inpatients residents in Monastir Governorate and admitted for community-acquired RI (URI and LRI) from 1 January 2002 to 31 December 2013. Admission criteria for all pathologies and ages were related to the severity of the clinical presentation or to an associated comorbidity.

Concerning pneumonia in pediatric age, the admission was systematic for children under 3 years of age, children with fever >39 and those with respiratory distress or associated comorbidities.

Health-care associated RIs were not included.

3.2. Variables

Register data involved socio-demographic variables such as age and gender. Variables related to hospitalization characteristics were admission dates, discharge diagnosis, entry mode, Length of Hospital Stay (LHS) and in-hospital deaths. Patients' diagnosis was provided at the hospital discharge.

Infectious or communicable diseases were defined as an illness caused by another living agent, or its products, that can be spread from one person to another [12].

In adults, the diagnosis of pneumococcal pneumonia (PP) was done on the identification of SP in blood cultures.

For pediatric age, the diagnosis of pneumonia was based on the clinical symptomatic triad (cough, fever and breathing difficulties) and chest x-ray. An etiological approach was adopted to differentiate between pneumonia with viral agent, atypical agent or bacterial agent (SP or Hib). To identify the bacterial etiology of pneumonia, blood cultures were an accurate way to determine whether the SP or Hib was the cause of pneumonia. Given that Hib culture requires special transport and growth conditions and that these cultures are only positive for a small proportion, the diagnosis of Hib pneumonia was retained in front of a compatible clinical presentation and negative blood culture for SP.

For immunization, vaccination against Hib was introduced in TEPI in October 2002 for children born after 1 July 2002. The Hib vaccine was provided as liquid Hib conjugate vaccine (monovalent form) and given at 3, 4, 6 months of life. Then, Hib vaccination was officially discontinued in November 2005 and reintroduced in April 2011 as Hib conjugate vaccine in the pentavalent vaccine combination (Hib, Hepatitis B, and DPT) [10]. Thus, three cohorts were defined as follows:

The not vaccinated cohort (NVC): hospitalized children born before July 2002 or those born after November 2005 to March 2011 were considered unvaccinated against Hib.

The first vaccinated cohort (VC) with monovalent form at age of 3, 4 and 6 months: hospitalized children born between July 2002 or those born before November 2005 were considered vaccinated with Hib monovalent vaccine.

The second VC with the pentavalent vaccine at age of 2, 3 and 6 months: all hospitalized children born after April 2011 were considered vaccinated with pentavalent vaccine.

3.3. Data sources

Data collected from the regional register of hospital morbidity were used. We selected RI from hospital morbidity data encoded according to ICD-10. Each

patient had a unique identifier. Patients' diagnosis was provided at the hospital discharge. More details are available elsewhere [13–15].

URI included otitis externa and acute otitis media (AOM) (H60-H62; H66-H67), mastoiditis and labyrinthitis (H70; H75; H83); acute nasopharyngitis, acute sinusitis, amygdalitis and flu (J00-J06, J09-J11) and phlegmonous angina, parapharyngeal abscess (J36; J39).

LRI included pneumococcal pneumonia (J13), pneumonia with Hib (J14), bacterial pneumonia, not elsewhere classified (J15), Pneumonia due to other infectious organisms, not elsewhere classified (J16), pneumonia during an illness classified elsewhere (J17), or with unspecified microorganism (J18), acute bronchitis (J20), acute bronchiolitis (J21), unspecified bronchitis (J40) and lung and mediastinum abscess, pleural empyema (J85, J86).

3.4. Statistical methods

3.4.1. Descriptive analysis
Data were verified, and analyzed using IBM SPSS Statistics version 22.0 software. Categorical variables (age group, sex, and mortality) were presented as effectives and percentages, quantitative variables by median and interquartile Range (IQR). Pearson chi2 was used.

3.4.2. Trends
Linear regression using the slope 'b' of the least-squares line and 'r' spearman coefficients were determined to estimate URI and LRI trends according to gender and age group. A p-value of <0.05 was considered statistically significant.

3.4.3. Standardization
Crude incidence rates (CIRs) of RI were calculated based on the Tunisian National Institute of Statistics and expressed in 100,000 inh [16]. The age-standardized incidence rate (SIR) per 100,000 person-years (PY) was calculated among the world standard population according to the WHO 2013 report [17]. Death parameters were fatality and age-standardized mortality rates (SMR).

3.4.4. Health burden
Disability Adjusted Life Years (DALYs) were calculated by the sum of years of life lost (YLLs) and years lived with disability (YLDs). YLD estimates are calculated by the equation (YLDs = Prevalent cases × Disability weight). Disability weights for GBD 2013 were derived from a pooled analysis of data from the GBD 2010 Disability Weights Measurement Study [18].

3.4.5. Impact of Hib immunization
To compare the unvaccinated cohort and the vaccinated one, we calculated absolute risk/100,000 inh, absolute risk reduction (ARR)/100,000 inh; relative risk (RR), relative risk reduction and number needed to treat (NNT) using Excel.

3.4.6. Ethical considerations
The data register was collected at hospital discharge, in accordance with international guidelines, national laws and local regulations, including data protection.

4. Results

4.1. Admission characteristics
During the study period, 6891 hospitalized RI were notified. Of them, 6061 were inhabitants of Monastir (87.9%) representing 17.6% (CI95%: 17.3–18.1) of all hospitalizations for communicable diseases. Hospitalization for LRI and URI represented, respectively, 76.3% and 23.7% of all hospitalized RI.

Thirty-one patients had three hospitalizations for RI and 400 patients had 2 hospitalizations. Two-thirds of RI inpatients were males. Sex-ratio was 1.12 for URI and 1.64 for LRI (p < 0.0001). At admission, the median age was 22 years (IQR: 3–52). It was 24 (IQR: 3–55) for males and 20 years (IQR: 3–47) for females (p = 0.004). The median age was 1.25 years (IQR: 1–1.50) for acute bronchiolitis and 31 years (IQR: 17–45) for otitis (p < 0.0001) (Figure 1).

The median length hospital stay (LHS) was 5 days (IQR 4–8 days) for URI and 6 days (IQR 4–9 days) for LRI. Emergency Department (ED) was the major entry mode of LRI. Most of patients with URI were admitted in otorhinolaryngology department (n = 1251,87.1%) and pediatrics department (n = 141,10%). As for patients with LRI, pediatrics and pulmonary departments took charge of 66.4% (n = 3072) and 23.7% (n = 1097) of admissions, respectively. Fifty-eight patients were admitted in intensive care during the period study.

4.2. Hospitalized RI incidence and mortality rates
For hospitalized URI, 1436 admissions were recorded (120 hospitalizations per year). The CIR was 24.19 per 100,000 inh. It was 31.9 for children aged up to 5 years and 21.9 for inpatients aged more than 60 years old. The age-SIR was 21.95 per 100,000 PY, 23.09 for men and 20.89 for women, respectively (Table 1).

For hospitalized LRI, 4624 admissions were recorded (385 hospitalizations per year). The CIR was 77.5 per 100,000 inh. It was 506.6 for children aged up to 5 years. The in-hospital fatality was 1.41%. The age-SIR was 71.63 per 100,000 PY, 90.2 for men and 53.6 for women, respectively. The SMR was 0.64 per 100,000 PY, 0.68 for men and 0.60 for women, respectively (Table 1).
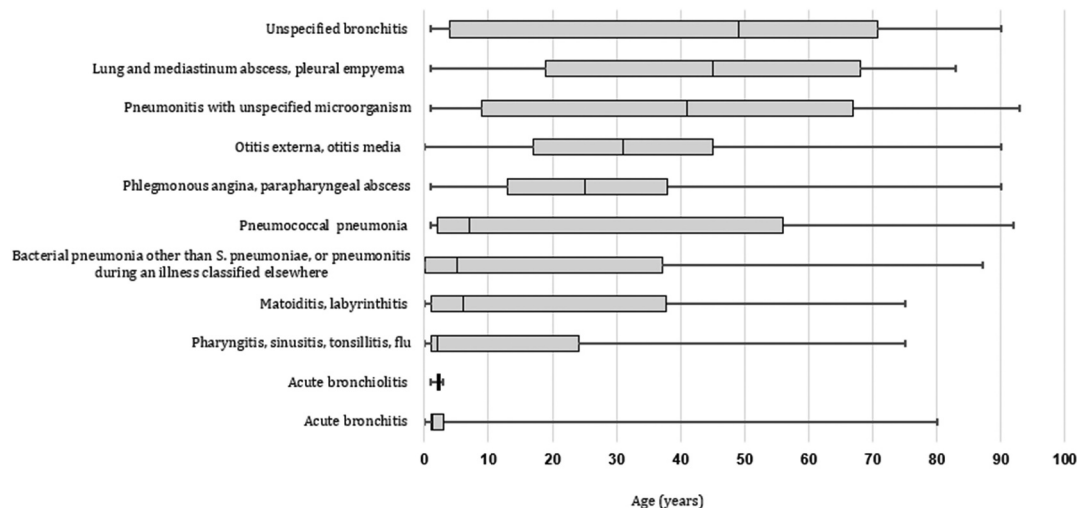
Figure 1. Age distribution of patients admitted for acute Respiratory Infections (Monastir; 2002–2013).

Legend: The half of pneumococcal pneumonia occurred in childhood (<18 years old)

Table 1. Crude and standardized incidence rates and death cases of hospitalization for upper and lower respiratory infection (Monastir; 2002 − 2013).

	Upper RI				Lower RI				
	Cases	CIR/ 10^5 inh	ASR/10^5 PY	Death cases$^\$$ (Fatality): n (%)	Cases	CIR/ 10^5 inh	ASR/10^5 PY	Death cases (Fatality): n (%)	A-SMR/ 10^5 inh
(2002–2013)	1436			1 (0.07)	4625			65 (1.41)	0.64
Age									
[0–5[	167	31.9		1 (0.6)	2653	506.6		32 (1.21)	
[5–24[	485	21.4			547	24.1		9 (1.65)	
[25–40[	342	23.8			213	14.8		1 (0.47)	
[40–60[	321	27.7			391	33.7		5 (1.28)	
≥ 60	109**	21.9			760**	152.7		18 (2.37)	
Valid	1424	24.19	21.9		4563	77.5	71.63		
Gender									
Males	761	25.2	23.09	1 (0.13)	2871	95,0	90.2	33 (1.15)	0.68
Females	675*	23.1	20.89		1753**	59,5	53.6	32 (1.83)	0.60

Missing values (age) = 73 (1.2%); $: only one case of death have been unregistered among upper RI; RI: Respiratory infections, CIR: Crude incidence rate; ASR: Age-standardized incidence rates, inh: inhabitants; PY: person year, A-SMR: Age-standardized mortality rates.* p < 0.05; ** p < 0.001; fatality (%) = (number of deaths/number of cases)*100.

4.3. Distribution and trends of admissions for RI

URI were mainly otitis in 66.2% of cases, of which 98% were AOM. Among inpatients aged up to 5 years, admissions for pharyngitis, sinusitis, tonsillitis and influenza were predominant. URI decreased significantly over time (b = −4.90, p < 0.000). It declined for both sexes and for all age groups (Tables 2 and 3). No season distribution was recorded for AOM (p = 0.328).

LRI represented 76.3% of all RI admissions (Figure 2). Acute bronchiolitis and pneumonia represented, respectively, 35.7% and 53.9% of LRI. Admissions for LRI increased greatly and significantly (b = 13.81, p < 0.0001) (Figure 3). Admission for pneumonia increased significantly during study period (b = 5.16; p < 0.0001) especially in children up to 5 years old (b = 5.53). Admission for PP increased significantly during study period (b = 25.9; p < 0.0001) especially in children under five (b = 10.6) and among inpatients aged more than 60 years (b = 6.0) (Tables 2 and 3). It was largely predominant in males (sex-ratio = 5.06; p < 0.0001) and

had no seasonal variation (p = 0.765). In children under 3 years, winter predominance was noted (p < 0.0001) for PP admissions (38.7%) and for bronchiolitis (53%). Admissions for Hib pneumonia were decreasing for both sexes and for all age groups. However, admissions for acute bronchitis (J20) increased in children aged under 5 years and decreased in the next age group [5–25 years old].

4.4. Burden of severe RI

We recorded 3250 YLLs and 4032 DALYs during study period representing 54.14 YLL and 69.71 DALYs per 100,000 inh per year. Bacterial pneumonia was responsible for 2190 DALYs corresponding to 38.93/100,000 inh every year, composed by 88% of YLLs and 12% of YLDs (Table 4).

4.4.1. Impact of Hib vaccine on admissions for RI in children aged less than 3years old

In children aged up to 3 years, Hib pneumonia admission CIRs per 100,000 were 11.6 in NVC, 10.6 in VC by protocol

Table 2. Distribution and trend of admissions for respiratory infections according to sex (2002 to 2013 Monastir Tunisia).

	All (n = 6061)		Males (n = 3631)		Females (n = 2428)		Sex-ratio
	N (%)	Slope (SE)	N (%)	Slope (SE)	N (%)	Slope (SE)	
Upper Respiratory Infections: Overall	**1436 (100)**	**−4.90 (0.14) ****	761 (100)	−2.50 (0.10)	675 (100)	−2.08 (0.13) **	1.12
Otitis externa, Otitis media	950 (66.2)	−2.67 (0.12) **	481 (63.2)	−1.43 (0.07) **	469 (69.48)	−1.14 (0.11) **	1.02
Mastoiditis, Labyrinthitis	60 (4.2)	−0.26 (0.01) **	30 (3.9)	−0.002(0.01)	30 (4.44)	− 0.21 (0.01) **	1
Pharyngitis, sinusitis, tonsillitis, flu	111 (7.7)	−0.32 (0.04) **	67 (8.8)	−0.14 (0.04) **	44 (6.51)	−0.11 (0.03) **	1.52**
Phlegmonous Angina, Parapharyngeal abscess	315 (21.9)	−1.65 (0.07) **	183 [24]	−0.93 (0.05) **	132 (19.55)	−0.62 (0.07) **	1.39
Lower Respiratory Infections: Overall	**4625 (100)**	**13.81 (0.61) ****	**2870 (100)**	**9.92 (0.48) ****	**1753 (100)**	**4.04 (0.38) ****	**1.64**
Pneumococcal Pneumonia (J13)	823 (17.8)	17.32 (0.14) **	542 (18.9)	12.1 (0.09) **	280 (16.0)	6.5 (0.5) **	1.93**
Other Pneumonias (J14, J15, J16, J17, J18)	1670(36.1)	−11.16 (0.11) **	1107(38.6)	−6.4 (0.06) **	653 (37.2)	−5.78 (0.05) **	1.69**
Acute bronchitis (J20)	137 (2.9)	0.80 (0.07) **	72 (2.56)	0.47 (0.05) **	65 (3.7)	0.49 (0.06) **	1.11
Acute bronchiolitis (J21)	1652 (35.7)	8.62(0.35) **	1022 (35.6)	3.85 (0.27) **	630 (35.9)	4.32 (0.33) **	1.62**
Unspecified Bronchitis (J40)	301(6.5)	−0.59 (0.13) **	191(6.65)	−0.11 (0.11)	110 (6.)	−0.08 (0.15)	1.74**
Lung and Mediastinum Abscess (J85), pleural empyema (J86)	42 (0.9)	0.06 (0.01) **	26 (0.9)	−0.003 (0.010)	15 (0.85)	−0.013 (0.014)	1.73**

*: p < 0.05; **: P ≤ 0.001, SE: Standard Error *; slope = b; p values calculated using the test of linear regression.

Table 3. Distribution and trend of admissions for respiratory infections according to age groups (Monastir; 2002–2013).

	[0–5[		[5–25[		[25–60[		≥ 60	
Age (years)	N (%)	Slope (SE)	N (%)	Slope (SE)	N (%)	Slope (SE)	N (%)	Slope (SE)
Overall: Upper Respiratory Infectious	167	−0.46 (0.19) *	485	−2.45 (0.14) **	663	−1.93 (0.11) **	109	−0.11 (0.08)
Otitis externa, otitis media	47 (28.14)	0.25 (0.08) *	325 (67.01)	−1.99 (0.11) **	492 (74.20)	−0.89 (0.10) **	80 (73.39)	−0.09 (0.06)
Mastoiditis, labyrinthitis	25 (14.97)	−0.13 (0.04) **	16 (3.29)	0.02 (0.02)	16 (2.41)	−0.06 (0.01) **	3 (2.75)	-
Pharyngitis, sinusitis, tonsillitis, flu	66 (39.52)	−0.54 (0.12) **	16 (3.29)	0.09 (0.02) **	23 (3.46)	0.039 (0.02)	3 (2.75)	-
Phlegmonous angina, parapharyngeal abscess	29 (17.36)	−0.03 (0.04)	128 (26.39)	−0.56 (0.07) **	132 (19.9)	−1.02 (0.05) **	23 (21.1)	0.00 (0.05)
Overall: Lower Respiratory Infectious	2676	18.52 (0.46) **	547	0.81 (0.08) **	604	0.26 (0.07)	759	2.31 (0.10) **
Pneumococcal Pneumonia (J13)	371(13.9)	12.8 (0.09) **	161(29.4)	3.3 (0.02) **	103(17.1)	3.3 (0.02)	188(24.7)	4.5 (0.03) **
Other Pneumonias (J14, J15, J17, J18)	487(18.2)	−7.33 (0.06) **	304(55.6)	−2.9 (0.02) **	408(67.5)	−2.9 (0.2)	571(75.2)	−2.37 (0.03)
Acute bronchitis (J20)	105 (3.92)	0.72 (0.05)	20 (3.55)	−0.12 (0.01) **	4 (0.66)	NA	6 (0.79)	NA
Acute bronchiolitis (J21)	1622 (60.61)	11.09 (0.30) **	NA	NA	NA	NA	NA	NA
Unspecified Bronchitis acute or chronic (J40)	86 (3.21)	−0.31 (0.05) **	32 (5.85)	0.21 (0.02) **	76 (12.58)	1.03 (0.04)	107 (14.09)	0.35 (0.04) **
Lung and Mediastinum Abscess (J85), pleural empyema (J86)	6 (0.22)	0.04 (0.01) **	7 (1.27)	0.02 (0.004) **	13 (2.15)	−0.01 (0.01) **	15 (1.97)	0.02 (0.04)

*: p < 0.05; **: P ≤ 0.001, SE: Standard Error, NA = non applicable
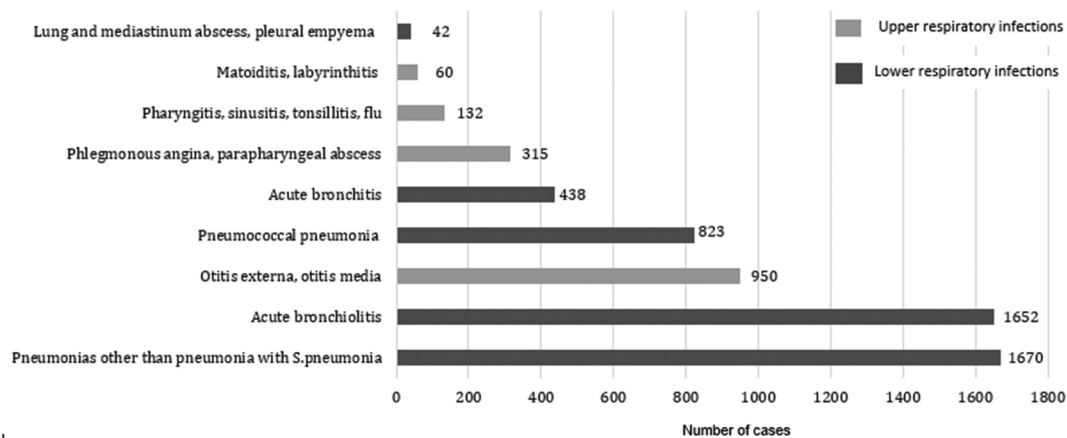
Figure 2. Distribution of admissions for acute respiratory infections (Monastir; 2002–2013).

Legend: Hospitalization for LRI was dominated by pneumonia while otitis represented the major causes of URI in the university hospital of Monastir (2002–2013).
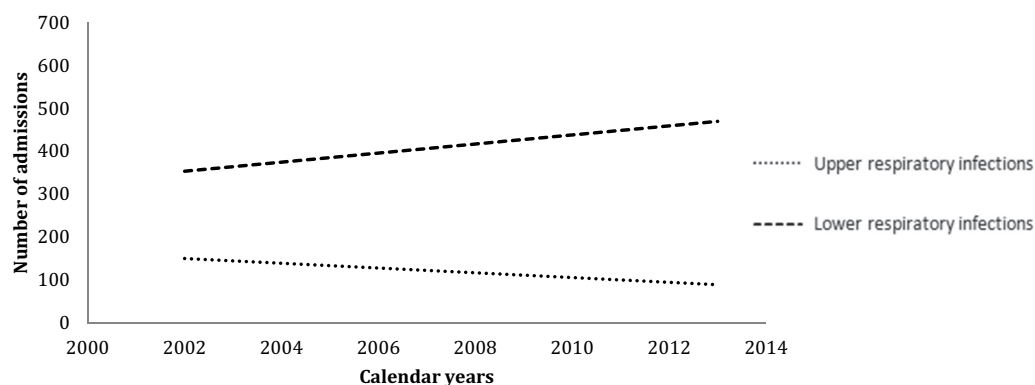
Figure 3. Trends of hospitalized upper and lower respiratory infections (Monastir, 2002–2013).
Legend: URI decreased and LRI increased significantly during study period.

Table 4. Burden of admissions for severe respiratory infections (Monastir; 2002–2013).

	YLL (%)	YLDs (%)	DALYs (%)	YLLs per 100,000 inh	YLDs per 100,000 inh	DALYs per 100,000 inh
All	3260.9	781.91	4032.31	54.14	3.51	**69.71**
Age group						
[0–5[	2599.0 (80.0)	375.1 (48)	2974.1 (73.8)	44.15	6.95	51.10
[5–25[	373.6 (11.5)	137.3 (17.6)	510.9 (12.7)	6.35	2.54	8.89
[25–40[	86.8 (2.7)	73.8 (9.4)	160.6 (4.0)	1.47	1.37	2.84
[40–59[	116.1 (3.6)	94.7 (12.1)	210.8 (5.2)	1.47	1.75	3.73
≥ 60	74.9 (2.3)	101.1 (12.9)	176.0 (4.4)	1.44	1.87	3.15
Gender						
Males	1541.9 (47.3)	483.0 (59.9)	2025.0 (49.8)	26.19	8.95	35.15
Females	1719.0 (52.7)	322.92 (40.1)	2041.9 (50.2)	29.20	5.98	35.19
Main RI categories						
Acute bronchiolitis	879.0 (26.9)	219.72 (27.3)	1098	14.93	2.77	17.7
Bacterial Pneumonia	1932(59.3)	259.09(32.2)	2190	32.83	6.10	38.93
URI and Other LRI	449.8 (13.8)	327.31 (40.6)	776	6.37	6.07	12.44

YLLs: years of life lost; YLDs: years lived with disability; DALYs: Disability Adjusted Life Years.

Table 5. Impact of Hib vaccine on admissions and in-hospital deaths related to respiratory infections among children aged under 3 years old.

		Cases	Population	Absolute risk * (95% CI)	ARR*	Relative risk (95% CI)	RRR (95% CI)	NNT	P
Hib Pneumonia									
Protocol 1	Vaccinated	121	1121344	10.7 (8.86; 12.71)	0.84	0.92 (0.74;1.15)			0.492
	Unvaccinated	261	2242688	11.6 (10.2; 13.0)					
Protocol 2	Vaccinated	9	1121344	0.80 (0.027; 1.30)	10.83	0.068 (0.035;0.13)	0.99 (0.94;0.99)	9230 (7773;11359)	< 0.0001
	Unvaccinated	261	2242688	8.17 (7.31;9.03)					
Acute otitis media									
Protocol 1	Vaccinated	11	1121344	0.98 (0.40;1.56)	0.49	0.66 (0.33;1.32)			0.24
	Unvaccinated	33	2242688	1.47 (0.96;1.97)					
Protocol 2	Vaccinated	5	1121344	0.44 (0.05;0.84)	1.02	0.30 (0.11;0.77)	0.69 (0.22;0.88)	9751 (55946;379283)	0.012
	Unvaccinated	33	2242688	1.47 (0.96;1.97)					
Deaths all causes aged <3 years									
Protocol 1	Vaccinated	2	1121344	0.17 (0.06;0.43)	0.83	0.16 (0.04;0.70)	0.83 (0.29;0.96)	112135 (65703;382310)	0.0149
	Unvaccinated	24	2242688	1.07 (0.64; 1.49)					
Protocol 2	Vaccinated	0	1121344	0	1.07	0.0408 (0.002;0.67)	0.99	95434 (60030;232629)	0.0252
	Unvaccinated	24	2242688	1.07 (0.64; 1.49)					

*: per 100,000 inh; unvaccinated cohort: patients born between 2005 and 2011; vaccinated by protocol 1: patients born between 2002 and 2005, with Hib monovalent vaccine at 3, 4, 6 months; vaccinated by protocol 2: patients born after 2011, with a Hib pentavalent combination vaccine at 2, 3 and 6 months; ARR: Absolute Risk Reduction; RRR: relative risk reduction; NNT: Number Needed to Treat

1 (Hib Vaccine monovalent) and 0.80 in VC by protocol 2 (Hib vaccine pentavalent combination), the relative risk reduction was 99% for protocol 2 (p < 0.001). AOM admission CIRs per 100,000 were 1.47 in NVC, 0.98 in VC by protocol 1 and 0.44 in VC by protocol 2, the relative risk reduction was 69% for protocol 2 (p < 0.001). The

relative risk reduction, for all in-hospital deaths related to RI in infants under 3, was 57% and 89% for protocol 1 and protocol 2, respectively (Table 5). For Hib pneumonia admissions sex-ratio was 1.27 for protocol one (p = 0.124), 1.40 for NVC (p = 0.006) and 1.25 for protocol 2 (p = 0.739) (Table 5).

5. Discussion

This study had as objectives to assess the trends and the health burden of hospitalized RI and their trends during a period of 12 years. The impact of Hib vaccine was also evaluated by comparing the VC and the NVC.

RI admissions accounted for approximately the fifth of all communicable disease hospitalizations, dominated by LRI. Children aged up to 5 years were the most affected. Otitis and bronchiolitis were the main diseases causing admission to university hospitals. Bacterial Pneumonia was the leading cause of YLLs.

In addition, we found that Hib vaccine had a significant impact on the reduction of RI-related hospital admissions and deaths in children up to 3 years.

Admission for LRI was higher than for URI, consistent with other studies conducted in hospital setting, qualifying LRI as the second cause of morbidity and the fourth leading cause of mortality in all age groups in 2013 with a high burden related to pneumonia [19–21]. However, URI has long been regarded as the most frequent RI in community [22].

According to the literature, AOM represented the most common admissions for URI and were frequent mainly in young people [23,24]. Hospital admission for AOM is a useful marker for otitis media severity [25]. AOM had a decreasing trend in our studies. However, it was increasing in other studies conducted in developed countries [25,26]. The homogeneous seasonal distribution of AOM admissions contrasted with the results of a study conducted in Taiwan that showed a peak from March to May, which could be related to climate differences [23]. Pharyngitis hospitalization rates were decreasing also in our sample due to the efficacy of Tunisian national program in preventing acute articular rheumatism and to the medical practice performance in primary care [27].

Similarly to literature, admissions for LRIs are predominant among men, children aged up to 5 years and the elderly [28]. This great difference in sex and age can be explained by the high prevalence of male smokers in Tunisia [29] and by chronic comorbidities, in particular COPD, proving the need to generalize the pneumococcal and influenza vaccines for this population [30].

A systematic analysis showed a consistently higher incidence of admissions for severe LRI in boys than in girls for all age groups [31]. The hypothesis to explain could be the evidence of smaller airway size in young boys than in young girls [32].

The seasonal variation was not observed in the rate of LRI admissions to the hospital. In other studies, the highest number of pneumonia cases occurred in winter and autumn [33,34]. Another data on the seasonality of influenza pneumonia in Thailand showed a sharp increase during the months of January through April [35].

Pneumonia was the most frequent cause of hospitalizations for LRI. The higher rates were seen in older adults and children <5 years old. The increasing trend of LRI was related in particular to PP which increased significantly during study period. A nationwide retrospective database analysis conducted from 2009 to 2016 in Poland showed the same results with an increasing trend of SP pneumonia and decreasing one for Hib pneumonia [36]. These trends could be explained by the vaccination status for both pathogens. In fact, in that period of time in Poland, pneumococcal conjugate vaccine (PCV) was not yet introduced in their national immunization program to protect children against invasive pneumococcal disease.

Our results showed that RIs increased mortality rather than disability especially for children. A systematic analysis for the Global Burden of Disease Study 2013 showed that for children, two causes each accounted for more than half a million deaths and collectively accounted for more than a third of deaths: lower respiratory infections, and malaria [37].

When comparing the health burden of RI by gender, we found that DALY were very close (2025.0 in males vs 2041.9 in females). It may be explained by YLL which was higher in females than in males given that the life expectancy at birth in females is higher than in males as well. However, males had more YLD than females.

Our study showed that immunization against Hib by the pentavalent form was more effective than the monovalent form. We found that admissions for Hib pneumonia in infants under 3 decreased significantly among the cohort vaccinated by the combined form of vaccine. This leads to the belief that the pentavalent form is more immunizing.

However, there is no conclusive evidence of differences in the immune response to monovalent or combined Hib conjugate vaccines. In fact, a review about the successes and the contribution of hexavalent combination Hib vaccines in Europe from 2000 to 2014; showed a higher acceptance. On the other hand, there are some concerns that this combined form may reduce Hib immunogenicity [38]. Our results may be related to the high Hib vaccine coverage among children born since 2011. This high coverage vaccine provided by combined vaccines is explained by the reduction of injections number for babies and the reduction of visits to healthcare centres.

In addition, the effect of Hib Conjugate Vaccine on the prevention of pneumonia in hospitalized infants for bronchiolitis was shown by a case-control study [39]. In NVC, male children dominated Hib pneumonia admissions whereas no sex-difference was notified in VC, this result was concordant with conclusions in literature [40].

Haemophilus influenzae serotype b is responsible for approximately 95% of all invasive disease (pneumonia or meningitis) due to Haemophilus influenzae. Other serotypes and non-encapsulated strains can cause otitis media in children and disease in the elderly and in immunocompromised populations [41,42]. As shown in our study, the introduction of Hib conjugate vaccines led to a major decline in levels of nasopharyngeal infections such as AOM [43]. This has led to a substantially greater reduction in disease incidence than can be directly attributed to the effects of the vaccine, suggesting that widespread use of the vaccine has resulted in the induction of herd protection [44].

The burden of RI may be more important than the result found. We recognize that many children could not receive hospital care, such as in other developing countries. In addition, our study did not include the secondary level health-care institutions which had weak capacity compared to the study area. Therefore, our regional estimates may underestimate the true burden of hospitalized RI [31].

6. Conclusion

Admissions for community-acquired RI were pronounced especially for the two extreme age groups. Our findings suggested that the introduction of Hib vaccine contributed greatly in reducing admissions for pneumonia and AOM. Immunization against Hib and more especially pentavalent combination vaccines had an impact on the admission and severity of RI in children. The recent introduction of anti-pneumococcal vaccine in the TEPI will improve this decrease and give a great contribution to alleviate the burden of RI [45,46]. In fact, a substantial reduction in hospitalization for pneumonia was observed after the introduction of PCV in many countries [28,45]. A national surveillance data must be more rigorous to determine immunization outcomes.

Disclosure statement

The authors declare that they have no competing interests.

Ethics approval

The study was approved by the Regional Scientific Ethical Committee (Monastir) since 1996 and re-approved in 2006.

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