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Etiologies of acute respiratory infections in children aged 1 to 59 months in Niger

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Abstract

Respiratory infections remain an important cause of morbidity and mortality in children worldwide. Children aged 1 to 59 months suspect of respiratory infections were enrolled with a view to determine the etiologies of infection and improving care. In total, 767 children were enrolled. The mean age and sex ratio male/female were respectively 13.25 months and 1.3. Children aged ≤12 months and those >12 months were respectively 136/767 (17.7%) and 631/767 (82.3%). The mean hospitalization time was 6.1 days (mini=0, max=20). Of the 767 children, 714 (93.1%) had at least one sign of severe infection detected with 325/714 (42.5%) having a body temperature ≥ 38°C associated. Procalcitonin level was significant in 173/633 children (27.3%) while Binax rapid test was positive in 176/642 (27.4%). The two tests agreed in 54/159children (34.0%). Blood culture was requested for 55/767 (7.2%) children and only 11 were positive with *Staphylococcus aureus* being the major etiology (63%) isolated. Etiologies detected by PCR from nasopharynx were *Streptococcus pneumoniae* (39.3%) and respiratory syncytial virus (23.6%) with 86 children co-infected by both pathogens. Other etiologies detected were *Staphylococcus aureus* (17.9%), Rhinovirus (10.1%), Adenovirus (9.4%), and Parainfluenza virus (7.3%). Sixty percent of children were fully vaccinated with pentavalent vaccine but only 10% received their second dose of PCV13 vaccine. Multiple home visits for post hospitalization health monitoring did not offer better prevention of morbidity and mortality compared to a single visit (*P >0.05*). A rate of 42.5% severe respiratory infections was detected with *Streptococcus pneumoneae* and Respiratory Syncytial Virus encountered the most.

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Introduction

Acute lower respiratory infections (ALRIs) are the primary killer of children in in low and middle income countries (Black *et al.*, 2003, Liu *et al*., 2015, Kyu *et al.,* 2015). Many children with ALRIs are not properly diagnosed, and are usually unjustifiably treated with antibiotics which contributes to the increase in drug resistance (Lim, 2006). Since 1990, considerable progress was made in the framework of Millennium Development Goals number 4 and significant decrease was obtained in morbidity and mortality of children under the age of five years. Infant death rate was reduced from 90.6 ‰ in 1990 to 43‰ in 2015 (Bhat and Manjunath, 2013, Noordam *et al*., 2015, Qazi *et al*., 2015, You *et al.,* 2015). Of the 6.3 million deaths of children in 2013, respiratory infections were responsible for 3.3 million (51.8%), including 14.9% due to pneumococcal pneumonia (Bryce *et al*., 2005). The absolute mortality rate of children under five years had decreased in sub-Saharan Africa, but this region urgently needs to step up its efforts, as it still accounts for almost half the deaths of children observed worldwide. Sub Saharan Africa is the only region where the numbers of live births and children under five years are both predicted to increase substantially in the next few decades (Bhat and Manjunath, 2013, You *et al.,* 2015). Diverse viral and bacterial etiologies can be responsible for respiratory infections. The principal viral causes are Respiratory Syncytial Virus (RSV), Rhinovirus, Adenovirus, Influenza and parainfluenza virus and human Metapneumovirus. Bacterial etiologies of respiratory infections include *Streptococcus pneumococcus* (Spn), *Haemophilus influenzae* type b *(Hib),* and *Staphylococcus aureus (S. aureus) (*Adiku *et al*., 2015, Liu *et al*., 2015*)*. In Niger, Lagare *et al.,* 2015 reported 35% and 56% severe respiratory infections in under five years children respectively caused by RSV and Spn. In addition to these etiologies, Cenac *et al.***,** 2002 had previously shown that *Clostridium pneumoniae* (*Cpn*) was associated with respiratory infections in 10 to 34-months-old children.

In Niger as in most sub-Saharan African countries, difficulties related to financial and sociocultural barriers, gender dynamics, and poor access to health centers limit efforts to mitigate child diseases particularly pneumonia (Bedford and Sharkey, 2014). Furthermore, respiratory infections are diagnosed on the basis of clinical symptoms due to limited resources and poor access to specialist care services, X-rays and clinical laboratory testing. Since effective and affordable treatment is available, effort should be made to improve access to health facilities and accurate laboratory diagnosis of infectious agents in children so as to contribute to achieving the WHO and UNICEF goal of eliminating preventable deaths due to pneumonia and diarrhea in countries with high infant mortality by 2025 (Noordam *et al*., 2015). The aim of the present study is to improve the integrated management of childhood illness (IMCI) through identification of etiologies of respiratory infections for an adapted treatment and testing of a new strategy for post hospitalization health monitoring.

Materials and methods

Study sites

This study was conducted in pediatric Departments A and B of Niamey National Hospital and in Pediatric Department of Lamordé National Hospital. These two institutions are reference hospitals and both are located in the capital city, Niamey. Pediatrics unit A of Niamey National Hospital receives sick infants aged up to two years, and Pediatrics unit B receives children aged three to 15 years. The Pediatric unit of Lamordé Hospital receives sick children from birth until the age of 15 years.

Population, Sample Collection and laboratory diagnosis

This study was prospective and descriptive conducted from January 2015 to June 2016. Children aged 1 to 59 months with signs of respiratory infection, hospitalized in one of the pediatric departments of the two hospitals, were enrolled.

Was considered having a severe infection, any child with a core body temperature≥ 38°C associated with at least one sign of respiratory disorder. Children over the age of five years and or suffering from heart disease or chronic respiratory infection were excluded. Blood cultures were performed using Bac T/Alert® PF medium (Ref. 259794, Bio Mérieux), which were incubated at 36±0.5°C in a Bac T/Alert 3D 60 Bio Mérieux 60 for 2 to 3 days, followed by bacteriological analysis on positive cultures. Urine samples were tested for Spn with rapid test Binax Now *Streptococcus pneumoniae* Antigen Card test (Ref: 710-000) and procalcitonin was determined with the BRAHMS PCT kit (reference 30450) on a VIDAS machine (Bio Mérieux, France).

Nasopharyngeal carriage of viruses and bacteria was assessed by qPCR, with the FTD Respiratory Pathogens 21+kit (Ref: FTD-2+1-32 Fast Track Diagnostics, Luxembourg SARL). Enrollment of participants was done in two phases: phase 1 consisted of two periods of two months each, one in the dry season and the other in the rainy season with post hospitalization follow-up of children for one month after successful treatment. Phase 2 was spread over one year to cover four seasons, the cold season from 15 December to 14 February 2015, the dry season (hot and dusty) from 15 February to 31 May 2015, the rainy season from June to September, and the warm and humid period from 1 October 1 to 14 December 2015. Data on sociodemographic factors were collected using a questionnaire addressed to parents or next of kin accompanying the child after a signed consent was obtained. Post hospitalization home visit for health evaluation was organized for two groups of children (G1 and G2). Children in G1 were visited three times: one month (M1), three months (M3), and six months (M6) after discharge, whereas those in G2 were visited only once six months after discharge, as indicated in the classical document for the integrated management of childhood illness (IMCI).

Data analysis

All data were stored in an Access 2007 database and analyzed with R Version 3.1.2 software (2014). Chi^2 test was used to compare means and frequencies. Risk factors for respiratory infections were analyzed using single and multivariable analysis by logistic regression model.

Ethics Statement

This study was conducted in accordance with good clinical practice (International Conference on Harmonization (ICH). The protocol was submitted to and approved by the National Consultative Ethics Committee (CCNE) of Niger through deliberation N° 0016/2013/CCNE of October 30th, 2013. The study protocol was also validated by the Clinical Research Committee of the Pasteur Institute (CNOC). The study required slightly more blood than required for usual care (a total volume of 3ml, adapted if necessary, according to the patient's weight and medical chart). Samples were collected by the hospital doctors who cared for the hospitalized children as part of their routine practice. The cost of care for each participant was covered by the study and includes hospitalization, medicines and post hospitalization visits. All information about the children was kept strictly confidential.

Results

Characteristics of the children

In total, 767 children under the age of five years were recruited of whom 184 (24%) were referred from other healthcare centers to the participating hospitals. The sex ratio (M/F) was 1.3.

The ages ranged from 1 to 54 months, with a mean of 26.2 months; mode=25. Hôpital National de Niamey (HNN) admitted 425/767 (55.4%) children in pediatric unit A (307/425, 72.2%) mostly aged < 24 months old and in pediatric unit B (118/425, 27.8%) for those aged from 36 to 59 months. Hôpital National Lamorde (HNL) had one pediatric unit and admitted 342 (44.6%) children aged between 1 to 59 months old (Table 1).

Table 1. Age-group distribution per pediatric unit of children aged 1 to 59 months hospitalized in 2015 for respiratory infections in two reference hospitals in Niamey.

Age (years)	HNNA	HNNB	HNL	Total
Age ≤ 2	307 (40%)	-	-	307
Age 3-5	-	118 (15.4%)	-	118
Age ≤ 5	-	-	342(44.6%)	342
Total	307	118	342	767

HNNA: Hôpital National de Niamey, service de pédiatrie A; HNNB: Hôpital National de Niamey, service de pédiatrie B; HNL: Hôpital National de Lamorde, service de pédiatrie.

Clinical Diagnosis

Upon admission, 714/767 (93.1%) children had at least one sign of acute respiratory infection with the most frequent being fast breathing (54.4% and 59.2% respectively for children ≤ 12 months and those >12 months), dyspnea (52.2%), productive cough (54.2), bronchial congestion (51.5%) and popping rail (48.5%) (Table 2).

Out of 714 children with severe signs of infection, 325/714 (42.5%) had a core body temperature of at least 38°C detected upon admission.

The Commonest histories of infections at least three months prior to enrollment were malaria (64.1%), malnutrition (16.8%), flu infection (8.2%), pneumonia (1.6%) and others (9.3%).

Table 2. Percent distribution of respiratory signs of infections detected in children ≤12 months and in those aged 12-59 months hospitalized in 2015 in Niamey, Niger.

Symptoms	Children ≤ 12 months n=136 (17.7%)		Children > 12 months n=631 (82.3%)		Total	%
	Number	%	Number	%		
Fever ≥ 38°C	54	7.0	271	35.3	325	42.5
Respiratory rate ≥ 40	-	-	343	54.4	454	59.2
Respiratory rate ≥ 50	111	81.6	-	-		
Dyspnea	68	50	332	52.6	400	52.2
Quite child Stridor	5	3.7	21	3.3	26	3.4
Paradoxical breathing	26	19.1	111	17.6	137	17.9
Nasal flaring	56	41.2	300	47.5	356	46.4
sibilant Rales	57	41.9	282	44.7	339	44.2
Crackles	69	50.7	305	48.5	374	48.8
Wheezing	20	14.7	87	13.7	107	14
Bronchial congestion	66	48.5	329	52.1	395	51.5
Dry cough	50	36.8	207	32.8	257	33.5
Productive cough	67	49.3	349	55.3	416	54.2

Laboratory diagnosis

To detect bacterial infection, 652/767 children (86.3%) were tested for procalcitonin (PCT) level and, 173/633 (26.5%) were positive (PCT level >= 2µg/l). Binax rapid test for detection of pneumococcal antigen in urine (Binax-pneumo) was used to test 642/767 (83.7%) children out of whom, 176 (26.6%) tested positive. PCT and Binax tests agreed in 54/105 (51.43%) children that were tested by both methods. Blood culture was requested for 55/767 (7.2%) children and only 11 (20%) were positive, allowing isolation of 7 *S. aureus* (63.6%). 2 *E. coli* (18.2%) and 2 *Enterococcus faecalis* (18.2%).

White blood count (WBC) for detection of infection were significant (N>6000 white blood cells/ml) in 454/680 (94.6%) children. Major etiologies detected by PCR on nasopharyngeal swabs were *Spn* (39.3%) and RSV A and B (23.6%). Other viral and bacterial agents detected from nasopharyngeal swab were *S. aureus* (17.9%), rhinovirus (10.1%), adenovirus (9.4%), parainfluenza virus (7.3%), influenza A virus (6.7%), coronavirus (6.4%), metapneumoviruses A & B (4.8%), Boca virus (3.4%), other viruses (3%), *Hib* (2.6%) and *Chlamydia pneumoniae (Cpn)* (0.3%).

Of the 258 children that tested positive for Spn by PCR on nasopharyngeal swabs, 83 (32.2%) had a positive test by Binax-pneumo. RSV test was positive in 86/258 (33.3%) children that were Spn positive by PCR. This represents the rate of co-infection by both etiologies in the nasopharynx. Infections by RSV and Spn were detected throughout the year and their frequencies were found changing with season of the year (Fi.1). Rate of nasopharyngeal infection by RSV alone with no bacterial cause associated was 16.7% (43/215).

Antibiotic treatment

Overall, 685/767 (89.3%) hospitalized children were treated with antimicrobials. The antibiotics used in monotherapy were ceftriaxone (221/685, 32.1%), amoxicillin + acid clavulanic (94/685, 13.7%), ampicillin (89/685, 13.2%), amoxicillin (72/685, 10.5%), erythromycin (58/67, 8.5%) and Ciprofloxacin (6/685, 0.9%). The most frequent combinations for bi-antibiotherapy were ampicillin-gentamicin (4.5%) and ceftriaxone-gentamycin (3.6%). We observed that out of 159 children with known treatment outcome, 15 (9.4%) died despite being treated with Ampicillin (2/15), amoxicillin (1/15), erythromycin (2/15) and ceftriaxone (11/15). However, we did not clearly determine whether these deaths were linked to treatment failure. It was found that only 4/16 (25%) of these patients were Spn positive by Binax test, 6/13 (53.8%) were positive for procalcitonin test and 4/15 (26.7%) were positive for *Staphylococcus aureus* by PCR. None was positive for RSV virus, influenza and parainfluenza virus. Conversely, it was found that 43/215 (16.7%) children were only infected by RSV but got treated with antibiotics.

Home visits for health monitoring

A group of children (G1) was followed up for one, three and six months after discharge from hospital (modified Integrated Management of Childhood Infection, IMCI) for health monitoring in comparison to a second group (G2) that was followed up only once 6 months after discharge (standard IMCI strategy). There was no significant difference found between the two methods with regard to prevention of post-hospitalization morbidity (*P=0,406*) and mortality (*P=0.466*) (Table 3).

Table 3. Comparison of 2 post hospitalization health monitoring strategies in children aged 1 to 59 months, hospitalized in 2015 for respiratory infections.

Patients	G1 (one home visit at 6 months after discharge)	G2 (three home visits at 1, 3 and 6 months after discharge)
Viewed	295/311 (95%)	289/312 (93%)
sick	62/295 (21%)	68/289 (24%)
Died	12/295 4. 1%)	16/289 (5. 5%)

($P_{morvidity}$-*value = 0.466;* $P_{mortality}$=0.406)

Discussion

Data on respiratory infections in under-five year's children are of great importance in sub-Saharan Africa for planning interventions, given the high infant mortality of this region. But, only few data on etiologies of these infections are available in Niger and those that have been collected are not sufficient enough to help improve the care and preventive strategies of respiratory infections in children .The present study population consisted of 17.7% (136/767) children aged 1 to 12 months and 82.3% (631/767) children aged 12 to 59 months. Overall, pneumonia was detected in 59.2% (454/767) based on abnormal respiratory rates.

The frequencies of clinically diagnosed signs of respiratory distress were between 3.7% and 54.2% (Table 2). These data are consistent with a 2016 global report identifying lower respiratory tract infections as a major cause of infant deaths (Liu *et al*., 2015).

We found that 26.6% of children with respiratory infection had a Binax-pneumo positive test. Though the test can be positive in case of carriage, this rate might represent the proportion of pneumoniae due Spn detected in this study.

This rate is lower compared to the 50% mean estimate for sub-Saharan Africa (Bedford and Sharkey, 2014). PCR on nasopharyngeal swabs detected *Spn* in 258/657 (39.3%), with 83/258 (32.2%) being confirmed in urines by Binax-pneumo test. This indicates the rate of pneumococcal antigen passage from nasopharynx to blood circulation, suspecting a possible implication of Spn in the cause of infection. RSV rate of infection detected was 23.6%, a bit lower than 47.6% and 35% respectively detected by Lagaré *et al.*, 2015 in Niger and by Ouedraogo *et al*., 2016 in Burkina Faso. It is however more than 18% reported in a study by Adiku *et al*., 2015 in Ghana.

Co-infection Spn-RSV detected from nasopharynx was 33.3% (86/258) with only 17.4% positive for Spn test in urines. This result should call for a careful interpretation of laboratory test because, not only Bianx-pneumo can test positive in individual carrying Spn, but also the respiratory illness can not exclusively attributed to viral or bacterial agent. In case of co-infection treatment for both is necessary. This study detected 16.7% rate of mono infection of nasophrynx by RSV alone with no bacterial cause associated. Without laboratory diagnosis, it was the proportion of children that would undergo unnecessary long course of antibiotherapy.

Similarly, it was found that 16.7% (43/215) of children tested negative for a bacterial infection by both PCR and Binax-pneumo tests but were prescribed a reatment with antibiotics mostly in combination of two or three. Viral respiratory infections were generally more frequent than bacterial infections (Wardlaw *et al*., 2006, Ouedraogo *et al*., 2016) though, in this study fluctuation was observed according to season of the year (Fig.1).

Our data showed how important is laboratory diagnosis to assure a successful treatment of respiratory infections specially in children admitted in hospitals.

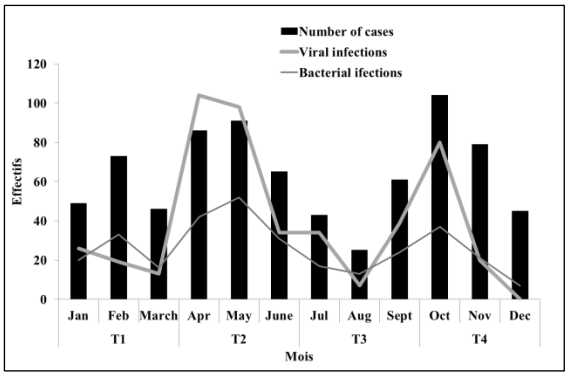

Fig. 1. Monthly evolution of viral and bacterial respiratory infections detected in 1-59 months children hospitalized in 2015 in two reference hospitals of Niamey, Niger.

In this analysis it was also foud that procalcitonin test, a marker of bacterial infection was positive in 26.5%, almost equally efficient with Binax-pneumo test (26.6%). The two tests agreed in 54/159 children (34%) tested by both methods. However, with regard to pneumococcal infection Binax-pneumo test would be preferable because it is specifique to pneumococci and easier to carry out. Combination of the two would offer greater advantage.

Hospitalization outcome was recorded for 180/767 (23.5%) children out of whom, 16/180 (8.9%) deceased. Four out of 16 deceased children (25%) tested positive for Spn with Binax-pneumo versus only 1 positive for RSV by PCR. Though the cause of death was not clearly determined, the detection of Spn in a number of death cases suggests the severety of child repiratory infection by this pathogen. It was aimed in this study to improve the strategy of health monitoring in children released after hospitalization. A modified protocole of integrated management of child illness (IMC) consisting of multiple home visits instead of only one and covering the parents' transport for return visits to hospitals. However, this strategy showed no significant difference ($P > 0.05$) compared to the standard IMCI procedure. The reason for this was that in developing coutries, child care depends on many factors including parents awareness and economic status.

In these countries, major obstacles were poverty, limited access to health services and reluctance of parents to promptly seek for medical care for their sick children at the first sign of an illness (Cenac *et al.,* 2002, Shi *et al.,* 2015). In addition, the loss of medical record and vaccination book complicates the task of healthcare providers in the post-hospitalization follow-up of children, as was found in this study.

Conclusion

A rate of 42.5% severe respiratory infection among 1-59 months children was found in the present study. Of the bacterial and viral etiologies, *S. pneumococcus* and respiratory syncytial virus rank first with pneumococcal infections being more prevalent than viral in cold and/or humid seasons. Systematic use of laboratory diagnosis and identification of etiologies of respiratory infections would improve treatment and increase chance of survival for affected children. The rapid Binax-pneumo test detects pneumococcal antigen in urine in 20 minutes. It can thus be a good point of care test for a rapid presumption of pneumococcal infection and help adapt treatment to the cause and reduce severe effect. PCR test detects and identifies both viral and bacterial causes of respiratory infections. The test offers a great advantage to reference hospitals for confirmation of viral or bacterial infection in about 4 hours or less. It can therefore be very helpful for treatment orientation. It was also found in this study that a successful prevention of post hospitalization morbidities and mortality did not depend on multiple home visits to patients by health personnel. Rather, conservation of medical records books and promptness of parents to seek for medical care are essential for the prevention of morbidity and mortality.

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