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Risk Factors for Death in Severe Acute Respiratory Infections Cases at the Houndé Sentinel Site, Burkina Faso

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Abstract

Background: In Burkina Faso, Acute Respiratory Infections are public health concern. It is one of the leading causes of death, but risk factors remain unknown. The objective of this study is to determine the risk factors for death in Severe Acute Respiratory Infections cases at the Houndé sentinel site from 2016 to 2019, in order to reduce the burden and the mortality of Acute Respiratory Infections in Burkina Faso.

Methods: We conducted a retrospective cohort study that covered the period from November 1, 2016 to June 30, 2019. We included, all cases of Severe Acute Respiratory Infections registered at the sentinel site of Houndé, which met the case definition of the RESPIRES project and benefited from a RT-PCR. For the statistical analysis, we performed a descriptive analysis of the cases, followed by a Cox regression which allowed us to calculate Hazard Ratios. Risk factors for death were sought at the $\alpha = 0.05$ threshold.

Results: We selected 503 cases of Severe Acute Respiratory Infections in the study. The median age of the cases was one year, with extremes of 6 days and 80 years. The sex ratio is 1.3. The median time of death was one day with extremes of 1 and 9 days. Four risk factors for death were identified: rural area [HR: 3.86; IC95% (1.23 - 12.06); p = 0.020]; *Parainfluenza* 1 virus [HR: 11.76; IC95% (2.41 - 57.30); p = 0.002], *Legionella pneumophila/Legionella longbeach* [HR: 17.08; IC95% (2.05 - 142.05); p = 0.009] and *Staphylococcus aureus* [HR: 3.54; IC95% (1.33 - 9.40); p = 0.011]. Antibiotic therapy during hospitalization [HR: 0.09; IC95% (0.01 - 0.70); p = 0.022] was also identified as protective factor.

Conclusion: Our results confirm the role of socio-demographic and biological factors in the occurrence of deaths in people with Severe Acute Respiratory Infections. Prevention through vaccination and the fight against the misuse of antibiotics through self-medication are effective ways to reduce mortality from Severe Acute Respiratory Infections.

Keywords: *Risk Factors for Death; Severe Acute Respiratory Infections; Bacteria; Virus; Public Health Concern; Sentinel Site; Burkina Faso*

Abbreviations

RESPIRES: Rapid Response and Surveillance of Respiratory Infections; RT-PCR: Real Time-Polymerase Chain Reaction; CMA: Medical Center with Surgical Antenna; OR: Obbs Ratio; HR: Hazard Ratio

Introduction

Acute Respiratory Infections are diseases of the upper or lower respiratory tract and can be caused by viruses, bacteria or fungi [1,2]. Worldwide, nearly 4 million people die each year from these diseases, 98% of which are due to lower respiratory tract infections [3]. Acute Respiratory Infections, particularly pneumonia, are the leading cause of death among children under five in developing countries, accounting for about 3 million deaths per year [4,5]. Similarly, these diseases are among the most common causes of admission in health care facilities and especially in paediatric services [6,7].

According to WHO, in 2015, lower respiratory tract infections were the leading cause of morbidity and mortality in Africa, with a crude mortality rate of 101.8 deaths per 100,000 population [8]. In Burkina Faso, Acute Respiratory Infections are one of the main causes of morbidity and mortality [9]. According to the health statistics of the Ministry of Health, in 2017, Acute Respiratory Infections were the second reason for external consultations in basic health training (25%) and the third reason for hospitalization in medical centers and hospitals. In addition, they were the third leading cause of death in medical centres and hospitals [10]. Sentinel surveillance of influenza and Acute Respiratory Infections was initiated in 2010 in Ouagadougou and Bobo-Dioulasso, with the support of the National Influenza Reference Laboratory (LNR-G) [11,12]. To date, there are 4 sentinel surveillance sites in Burkina Faso, namely, the Medical Center with Surgical Antenna (CMA) of Boussé, the CMA of Houndé, that of Kongoussi and the University Hospital Center (CHU) of Bogodogo.

In Senegal, Sonego *et al*. (2015) conducted a systematic review and meta-analysis of mortality risk factors for low Acute Respiratory Infections in children under five in low- and middle-income countries [13]. It was found that the diagnosis of very severe pneumonia as defined by the WHO [OR: 9.42; CI 95%: (6.37 - 13.92)], the age less than two months [OR: 5.22; CI 95% (1.70 - 16.03)], the diagnosis of *Pneumocystis carinii* [OR: 4.79; IC 95% (2.67 - 8.61)], underlying chronic diseases [OR: 4.76; 95% CI (3.27 - 6.93)], HIV/AIDS [OR: 4.68; 95% CI (3.72 - 5.90)], severe malnutrition [OR: 4.27; 95% CI: (3.47 - 5.25)], young maternal age [OR: 1.84; 95% CI (1.03 - 3.31)], low maternal education [OR: 1.43; 95% CI (1.13 - 1.82)], low socio-economic status [OR: 1.62; 95% CI (1.32 - 2.00)], exposure to second-hand smoke [OR: 1.52; 95% CI (1.20 - 1.93)] and indoor air pollution [OR: 3.02; 95% CI (2.11 - 4.31)] were risk factors for mortality [13]. Ndeye., *et al*. (2019) showed that comorbidity was significantly associated with the occurrence of death in children 3 months to 15 years of age [14].

In Burkina Faso, studies have also been conducted on Acute Respiratory Infections, but the majority have consisted of either a description of the clinical epidemiological profile, an etiological study, or the study of Acute Respiratory Infections of viral etiology [15-20]. In addition, the risk factors for Acute Respiratory Infections deaths were almost never addressed. Only one author addressed factors associated with mortality of Acute Respiratory Infections of viral etiology [20]. Finally, a quick analysis of the Acute Respiratory Infections National Sentinel Monitoring Base found that the Houndé and Kongoussi sentinel sites recorded more deaths (72% of deaths) from 2016 to 2019.

Objective of the Study

The objective of this study is to determine the risk factors for death in Severe Acute Respiratory Infections cases at the Houndé sentinel site from 2016 to 2019, in order to reduce the burden and the mortality of Acute Respiratory Infections in Burkina Faso.

Materials and Methods

Framework for the study

The Medical Center with Surgical Antenna (CMA) in Houndé served as the framework for the study ; it is the reference center of the health district of Houndé. The surveillance data were collected at the level of the Epidemiological Surveillance Service (SSE) of the Directorate of Population Health Protection (DPSP) and also at the National Influenza Reference Laboratory (LNR-G).

Type of study

This was a retrospective cohort based on secondary surveillance data of Severe Acute Respiratory Infections cases, enrolled at the Houndé sentinel site, from November 1, 2016 to June 30, 2019. The study itself took place from January to June 2020.

Study population

The study population consisted of all Severe Acute Respiratory Infections cases enrolled at the Medical Center with Surgical Antenna (CMA) in Houndé, and recorded in the severe acute respiratory infections national sentinel surveillance base, during the study period. Included in this study are the cases of severe acute respiratory infections:

- Enrolled only at the Houndé sentinel site during the study period;
- Meeting the case definition of the RESPIRES project during the study period (fever or history of fever, cough, maximum 10-day symptom delay and hospitalization);
- And has received RT-PCR for etiological diagnosis.

Collection tools and techniques

Existing data from the Severe Acute Respiratory Infections National Sentinel Surveillance Database were used and an Excel data extraction sheet was used as collection tool.

Definition of variables

We have chosen as a dependent variable (or explained), the evolution of Severe Acute Respiratory Infections cases that can be either healing or death. A case of death was any case of Severe Acute Respiratory Infections in which the variable «resulting from the case» was filled in «deceased» with a specific date ; the cured case complied with the same condition but with the only difference that in his case the outcome was marked «cured».

The independent variables were the risk factors for death selected for the study as:

- Socio-demographic characteristics: Age, sex, environment of residence, district of residence and occupation;
- Clinical and hospitalization characteristics: The time of consultation, the presence of signs of danger (dyspnea, inability to drink or suck, costal or stridor pull in, lethargy or unconsciousness, vomiting all, seizures or history convulsions, polyps, O_2 < 90% saturation), antibiotic therapy before and during hospitalization, oxygen therapy, history of chronic diseases, malnutrition, smoking, influenza vaccine status, the future of the case, the length of hospital stay;
- Biological characteristics (33 pathogens sought): Bacterial, viral and fungal pathogens, bacterial-virus co-infection;
- Seasonal and climatic data: Dry (October-May) and rainy (June-September) seasons.

Statistical analysis

The etiological analysis consisted of a survival analysis through the Cox model was performed. Thus the following parameters were considered for data reporting:

- The date of hospitalization as the date of origin;
- The date of the patient's birth as the date of the latest news;
- 10^{th} day of hospitalization as a peak date;
- A follow-up time of 10 days from the date of hospitalization.

The follow-up time being 10 days, all survivors after this time were censored to the right. As for those whose outcome was "in treatment or unknown" before the 10 days, they were considered lost of sight, thus censored to the left.

Cox regression was performed to look for risk factors for death:

- The univariate analysis made it possible to calculate the gross Hazard ratio (HR) of association between the death and the set of explanatory variables. All factors whose threshold (α) was 20% or less, as well as our variable of interest were retained for the continuation of the analysis;
- Multivariate regression was conducted by the step-by-step method. It obtained the adjusted Hazard ratios and their IC95% in the final model. For the interpretation of significance, the α = 5% threshold was used.

The data was analyzed using STATA® version 15.1 software.

Ethical approval

Patient consent was obtained and anonymity was preserved by assigning identification number. This study received ethical clearance from Health Research Ethical Committee (CERS) of Burkina Faso.

Results

Selection of the sample

Over the study period, 532 Severe Acute Respiratory Infections cases were recorded at the Houndé Sentinel site. We first excluded 6 cases (1.1%) that did not meet the Severe Acute Respiratory Infections case definition of the RESPIRE project. Then we excluded 18 cases (3.4%) for RT-PCR not performed. Of the 508 cases with RT-PCR, 7 (1.3%) were excluded for missing data. Finally, 503 cases of Severe Acute Respiratory Infections were selected for this study.

Description of the study cases

The median age of the cases was one (1) year for both sexes, with extremes of 6 days and 80 years and 6 days and 75 years, respectively, for the male and female sexes. Children under 5 were the majority age group, at 82%. The sex ratio was 1.33. More than half of the cases were in urban areas (51%). The average length of hospitalization was 3.07 ± 0.11 days. The median time of death was one (1) day (1 and 9 days) and deaths were approximately 4%.

Risk factors for death in univariate analysis cases

The univariate analysis identified 6 risk factors for death, the main ones being : rural area [HR: 4.141; IC95% (1.382 - 12.406); p = 0.004]; *Parainfluenza* 1 virus [HR: 7.924; IC95% (1.809 - 34.704); p = 0.032]; *Staphylococcus aureus* [HR: 2.598; IC95% (1.057 - 6.382); p = 0.047]; *Legionella pneumophila/Legionella longbeach* [HR: 26.191; IC95% (3.452 - 198.681) p = 0.033]. The results of the univariate analysis of risk factors for death in Severe Acute Respiratory Infections at the Houndé sentinel site from 2016 to 2019 are recorded in table 1.

Factors	**Haz. Ratio Brut**	**IC 95%**	**p-value**
Area of residence			0.004***
Urban areas	1		
Rural areas	4.141	1.382 - 12.406	
Consultation period			0.017**
No	1		
Yes	6.295	0.839 - 47.195	
***Parainfluenza* 1 virus**			0.032**
No	1		
Yes	7.924	1.809 - 34.704	
Staphylococcus aureus			0.047**
No	1		
Yes	2.598	1.057 - 6.382	
***L. pneumophila/L. longbeac*h**			0.033**
No	1		
Yes	26.191	3.452 - 198.681	
Klebsiella pneumoniae			0.047**
No	1		
Yes	2.476	0.987 - 6.212	

***Table 1**: Risk factors for death in univariate analysis of Severe Acute Respiratory Infections cases, Houndé Sentinel Site, 2016-2019, Burkina Faso.*

****: p < 0.01; **: p < 0.05; Haz. Ratio: Hazard ratio; IC 95%: 95% confidence interval.*

Risk factors for death in multivariate analysis cases

The final model identified: 4 risk factors for death : rural area [HR: 3.857; IC95% (1.233 - 12.063); p = 0.020]; *Parainfluenza* 1 virus [HR: 11.762; IC95% (2.414 - 57.298); p = 0.002]; *L. pneumophila/L. longbeach* [HR: 17.083; IC95% (2.054 - 142.052); p = 0.009] and *Staphylococcus aureus* [HR: 3.538; IC95% (1.332 - 9.400); p = 0.011] and 1 protective factor antibiotic therapy during hospitalization [HR: 0.086; IC95% (0.010 - 0.703); p = 0.022]. The results of the multivariate analysis of risk factors for death in Severe Acute Respiratory Infections at the Houndé sentinel site from 2016 to 2019 are recorded in table 2.

Factors	Haz. Ratio Ad.	IC 95%	p-value
Area of residence			0.020**
Urban areas	1		
Rural areas	3.857	1.233 - 12.063	
Antibiotic therapy during hospitalization			0.022**
No	1		
Yes	0.086	0.010 - 0.703	
***Parainfluenza* 1 virus**			0.002***
No	1		
Yes	11.762	2.414 - 57.298	
Staphylococcus aureus			0.011**
No	1		
Yes	3.538	1.332 - 9.400	
L. pneumophila/L. longbeach			0.009***
No	1		
Yes	17.083	2.054 - 142.052	
***Haemophilus influenza*e**			0.130
No	1		
Yes	0.473	0.180 - 1.245	

Table 2: *Risk factors for death in multivariate regression Severe Acute Respiratory Infections cases, Houndé Sentinel Site, 2016 - 2019, Burkina Faso.*

****: p < 0.01; **: p < 0.05; Haz. Ratio Ad: Adjusted Hazard Ratio; IC 95%: 95% Confidence Interval.*

Discussion

Socio-demographic risk factor

According to our study, living in rural areas increases the risk of death by about 4 times compared to urban areas. On the one hand, this result could be explained by the fact that in the province of Tuy (of which Houndé is the chief town), the rural population is strongly represented (65.9% vs 34.10%) [21]. On the other hand, rural patients often face certain difficulties that could aggravate their health, and therefore lead to death. These difficulties include poverty, precarious conditions of hygiene and certain socio-cultural practices (recourse to tradipraticians, the use of wood or charcoal as sources of energy and in concessions, the practice of bush fires). Added to this is the geographical inaccessibility of health centres, often associated with the precarious conditions of transport of the patient to the health centre. In our case, the CMA, which is the reference centre for the Houndé health district. For example, a patient residing in an urban setting will be more likely to have access to care than a patient living in a rural setting. In order to reduce this inequality in access to health care, the government adopted and implemented in 2016 a policy of free care for children under five and pregnant women [22]. However, efforts remain to ensure the sustainability of this intervention.

Ilboudo (2019) in Burkina Faso found that rural patients were less likely to develop a serious form of Severe Acute Respiratory Infections compared to urban patients [OR: 0.64 ; IC95% (0.49 - 0.85); p = 0.002], during viral Severe Acute Respiratory Infections [20]; result that seems to be contradictory to ours. This difference could be explained by the difference in study populations (Houndé Vs Burkina Faso) and also by the fact that this latest study was limited to viral Severe Acute Respiratory Infections.

Biological risk factors

The study showed that *Staphylococcus aureus* increased the risk of death more than 3 times. This result could be explained by the virulence of the germ and also by host-related factors including local immunosuppression, due to the presence of viruses in the respiratory tract [23]. Indeed, *Staphylococcus* aureus is known for its ability to cause necrotizing pneumonia [23]. And these pathologies are associated with the production of a particular toxin, Panton-Valentine leucocidine, involved in lung necrosis, the occurrence of hemoptysis, leukopenia, and high mortality [23]. This condition is rare and particularly affects adolescents or young adults [23]. It also occurs in a post-influenza context [23].

Another peculiarity of this germ, is its ability to resist meticillin, giving it the name of *Staphylococcus aureus* resistant to meticillin [24]. This risk would be due to the administration of antibiotics during the hospital stay, which exerts selection pressure by eliminating normal flora, especially sensitive *Staphylococcus aureus* [24]. In addition, this germ is responsible for acute sinusitis, community pneumonia and also nosocomial pneumonia [2,24,25]. It should be noted that mortality of nosocomial pneumopathies to *Staphylococcus aureus* remains significant (30 and 70%), despite appropriate management [24]. This mortality is greater in bacterioemic patients [26] and also in the presence of *Staphylococcus aureus* resistant to meticillin [24]. Randolph., *et al.* (2012) found in their study that children co-infected with *Staphylococcus aureus* resistant to meticillin were 8 times more likely to die during the Influenza A H1N1 pandemic than those infected with the virus alone [27].

Human *Parainfluenza* viruses exist under 4 serotypes numbered from 1 to 4 [28]. They cause respiratory diseases in children and adults, such as otitis media, pharyngitis, conjunctivitis, croup, tracheobronchitis, and pneumonia [28]. In the United States, *Parainfluenza* 1 virus generally causes biennial outbreaks during odd years, during the fall, and may be responsible for 50% of croup cases during epidemic seasons [28]. Although less common than serotype 3, studies have shown that during years of epidemics, *Parainfluenza* 1 virus was associated with a significant burden of morbidity and hospitalization in children [28,29]. Hung., *et al.* (2017) in Japan, found that *Parainfluenza* 1 virus infection in adults was associated with significantly higher mortality and longer hospitalization compared to influenza virus infection [30]. In addition, Fiore., *et al.* (1998) demonstrated that a recent infection with *Parainfluenza* 1 virus was significantly predisposed to the subsequent development of pneumonia and bacterial infections, which can often be fatal [31]. Thus, given the strong involvement of these viruses in children and adults Acute Respiratory Infections, we believe that the development of effective vaccines and antiviral drugs is therefore a necessity, in order to reduce their incidence and mortality. Today, candidates for vaccines against this virus are reportedly being tested [28].

According to our study, infection with *Legionella pneumophila/Legionella longbeach*, increases significantly, the risk of death 17 times in cases of Severe Acute Respiratory Infections. As a reminder, *Legionella* disease is an infection caused by a bacterium present mainly in water where it survives by parasitizing amoebae [32]. It can manifest either by pneumonia, more exceptionally by extra-pulmonary forms, with various locations (neurological, cardiac, muscular, joint) or by Pontiac fever [33]. It should be noted that *Legionella* infection is a serious infection and that the majority of patients are hospitalized (98.5%), with more than 1/4 in resuscitation [33]. It is responsible for approximately 10% mortality in the general population, 10% to 14% in transplants patients, and up to 50% in resuscitation hospitalization [33]. Given the rarity of this infection in children, who make up the majority of cases in our study, we can explain this result, by immunosuppression or by the presence of danger signs, in cases or through the acquisition of nosocomial infection during hospitalization. Ilboudo (2019) in Burkina Faso also found the same result [20].

Protective factor

Our results also showed that antibiotic therapy during hospitalization, on the other hand, was a protective factor in the occurrence of death in the cases in the study. This finding is apparent from the fact that almost all cases in the study (99%) received antibiotic treatment during hospitalization. This could be explained by the relatively high charge of bacteria compared to viruses in the study cases (92%

vs 78%). Antibiotic therapy, when properly prescribed, is intended to improve the patient's condition and prevent complications ; even death. However, this result should be considered with caution. Indeed, antibiotic treatment is not always systematic during Severe Acute Respiratory Infections, due to the frequency of viruses compared to bacteria [2]. In addition, the misuse of antibiotics promotes the selection of resistant strains of bacteria, known as antibiotic resistance. And this phenomenon is growing worldwide.

In this study, we found 4 risk factors for death in cases, including 1 socio-demographic factor that is the rural residence and 3 pathogens. Although these results do not concern ¼ sentinel sites, they could be extrapolated to the whole of Burkina Faso, because the ¾ of the « Burkinabè » population is rural and also the epidemiological similarity of isolated pathogens.

Conclusion

The objective of this study is to determine the risk factors for death in Severe Acute Respiratory Infections cases at the Houndé sentinel site from 2016 to 2019, in order to reduce the burden and the mortality of Acute Respiratory Infections in Burkina Faso. Our findings indicate that rural areas, *Parainfluenza* 1 virus, *Legionella pneumophila/Legionella longbeach* and *Staphylococcus aureus* are risk factors for death in these cases. The study also highlighted a protective factor that is antibiotic therapy during hospitalization. Our results highlight the importance of socio-demographic and biological factors in the occurrence of deaths in Severe Acute Respiratory Infections cases. Therefore, a special interest must be put on these 3 pathogens, in order to reduce the morbidity and mortality of Severe Acute Respiratory Infections in Burkina Faso. In addition, the strengthening of care systems at the peripheral level, combined with the improvement of the living conditions of rural populations, is necessary to achieve good results.

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Conflict of Interest

No conflict of interests is declared.

Author's Contribution

Dieudonné Tialla, Sonia Rouamba/Ilboudo, Assana Cissé and Zékiba Tarnagda have contributed equally to the work of this article.

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