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Acute lower respiratory infections on lung sequelae in Cambodia, a neglected disease in highly tuberculosis-endemic country

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Summary
Background: Little is known about post-infectious pulmonary sequelae in countries like Cambodia where tuberculosis is hyper-endemic and childhood pulmonary infections are highly frequent. We describe the characteristics of hospitalized Cambodian patients presenting with community-acquired acute lower respiratory infections (ALRI) on post-infectious pulmonary sequelae (ALRIPS).
Methods: Between 2007 and 2010, inpatients ≥15 years with ALRI were prospectively recruited. Clinical, biological, radiological and microbiological data were collected. Chest radiographs were re-interpreted by experts to compare patients with ALRIPS, on previously healthy lungs (ALRIHL) and active pulmonary tuberculosis (TB). Patients without chest radiograph abnormality or with abnormality suggestive as other chronic respiratory diseases were excluded from this analysis.
Results: Among the 2351 inpatients with community-acquired ALRI, 1800 were eligible: 426 (18%) ALRIPS, 878 (37%) ALRIHL and 496 (21%) TB. ALRIPS patients had less frequent fever than other ALRI ($p < 0.001$) and more productive cough than ALRIHL ($p < 0.001$). *Streptococcus*

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pneumoniae, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* accounted for 83% of ALRIPS group positive cultures. *H. influenzae and P. aeruginosa* were significantly associated with ALRIPS compared with ALRIHL. Treatment was appropriate in 58% of ALRIPS patients. Finally, 79% of ALRIPS were not recognized by local clinicians. In-hospital mortality was low (1%) but probably underestimated in the ALRIPS group.

Conclusion: ALRIPS remains often misdiagnosed as TB with inappropriate treatment in low-income countries. Better-targeted training programs would help reduce the morbidity burden and financial costs.

Introduction

The United Nations Millennium Development Goals aim to reverse the tuberculosis (TB) epidemic by 2015 [1]. Despite a clear reduction in TB incidence between 2010 and 2011, post-TB pulmonary sequelae remain under-recognized in most countries. The direct link between the number of TB episodes and lung damage is well documented [2]. In addition, widespread lung destruction may occur in spite of effective anti-tuberculous therapy. Subsequent healing may result in extensive fibrosis, bronchostenosis, pleura remodeling with loss of pulmonary volume and traction bronchiectasis [3]. According to the *World Health Organization* (WHO), Cambodia was the country with the highest documented TB prevalence worldwide at 817/100 000 population in 2012 [1]. Other under-treated bacterial infections such as pulmonary abscesses or purulent pleurisies may also cause pulmonary and/or pleural sequelae. Finally, bronchiectasis may result from acute lower respiratory infections (ALRI) with both tuberculous and severe non-tuberculous pathogens, which are highly prevalent in Cambodian children [4].

Surveillance of ALRI (the SISEA project, Surveillance and Investigation of Epidemics in South-East Asia) conducted in two Cambodian provincial hospitals found a high proportion of pulmonary sequelae diagnosed by systematic chest radiographs [5]. Local clinicians were unaware of this form of chronic respiratory disease. As such — and in absence of systematic microbial identification - patients are denied appropriate antibiotics and usually referred to a specialized TB ward for a standard 6-months anti-TB therapy. We undertook this study to describe the clinical, radiological and microbiological characteristics of patients presenting with ALRI on post-infectious pulmonary sequelae (ALRIPS) included in the project, comparing them to other types of ALRI; the management of ALRIPS patients is also discussed.

Methods

Data from patients in this study were prospectively collected through the community-acquired ALRI surveillance SISEA from April 2007 to July 2010 in two provincial Cambodian hospitals. This surveillance project focused on ALRI epidemiology in Cambodia, a Southeast Asian tropical country. The patient recruitment and assessment methodology is described elsewhere [5—8]. SISEA was approved by the Cambodian National Ethics Committee for Health Research (number 024-NECHR). Patients' informed consent was obtained prior to any investigation.

Briefly, after including inpatients with lower tract respiratory symptoms for less than 14 days and excluding patients with known immunodeficiency [5—7], hospital physicians recorded demographic, clinical, and therapeutic data as well as on-site biological testing results and outcome. They assigned a final diagnosis to each patient, including that of lung sequelae superinfection. On admission, blood, non-induced sputum, throat and nasopharyngeal samples were collected for direct examination, cultures and molecular diagnostic techniques, performed at Institut Pasteur du Cambodge. Procedures for viral and bacterial assessment have previously been described [6,7,9—12]. Direct sputum examination for acid-fast bacilli (AFB) were performed at the hospital laboratories for each patient on admission and repeated during the following two days. In accordance with Cambodia's national TB recommendations, culture was not systematically performed. A single chest radiograph per patient was performed on admission. Expert pulmonologists blinded to the patient's condition re-interpreted chest radiograph and then reviewed patients' medical files to assign a final diagnosis to each included case.

We extracted from the SISEA database adult patients (aged 15 years and above) with ALRI and abnormal chest radiograph on admission. We then excluded from analysis patients with other respiratory diseases such as pulmonary fibrosis, post-tobacco emphysema, pneumothorax and thoracic deformation. We thus classified patients into three groups: ALRIPS, ALRI on presumed previously healthy lung (ALRIHL), and pulmonary TB. We finally excluded patients with positive AFB smears and pulmonary sequelae to avoid confusion in groups' comparison (Fig. 1).

The ALRIPS group was defined as patients with clinical and biological signs compatible with ALRI and presenting post-infectious pulmonary sequelae on chest radiograph on admission. Post-infectious pulmonary sequelae were defined as radiologically-diagnosed lung lesions highly suggestive of a previous lung infection such as TB, abscesses, purulent pleurisies or bronchiectasis. Severe sequelae were defined by at least combination of two features such as retraction, pleural thickening, fibrosis, bronchiectasis and cavities. Fig. 2 illustrates severe sequelae. Moderate sequelae were defined by the above features taken separately.

The ALRIHL group was defined as patients with clinical, biological and radiological signs compatible with pneumonia, pleurisy, pleuro-pneumonia or pulmonary abscess and chest radiograph showing no signs of post-infectious sequelae.

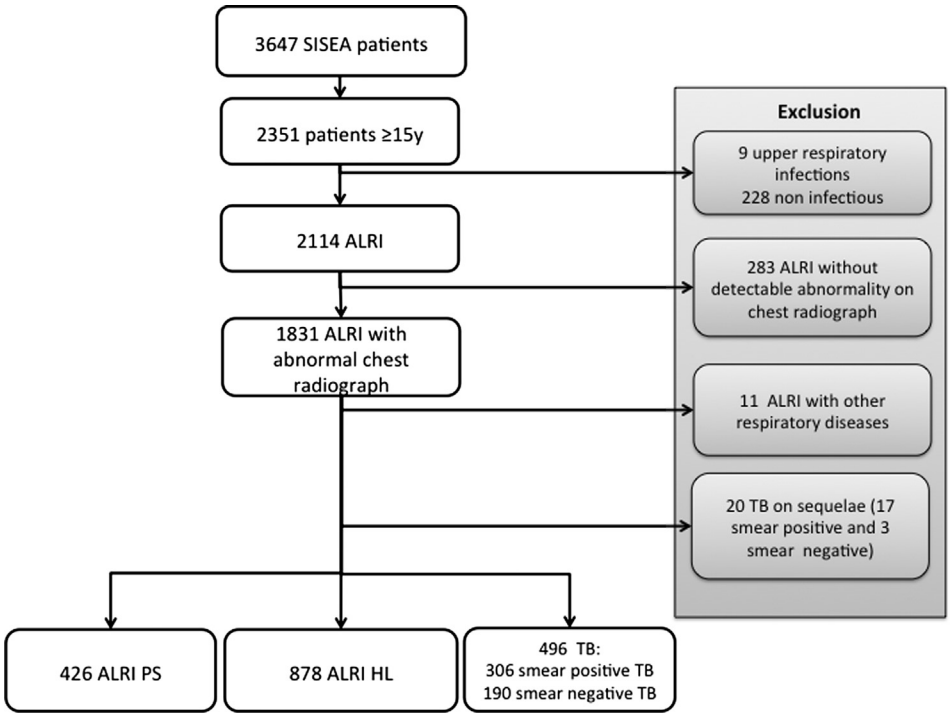

Figure 1 Flow chart of patient' inclusions for the post-infectious pulmonary sequelae superinfections analysis, SISEA study, Cambodia, 2007—2010.

As recommended by WHO, pulmonary TB, was confirmed by bacteriology or diagnosed by a clinician [13]. Smear-positive and smear-negative cases met the WHO definition [13].

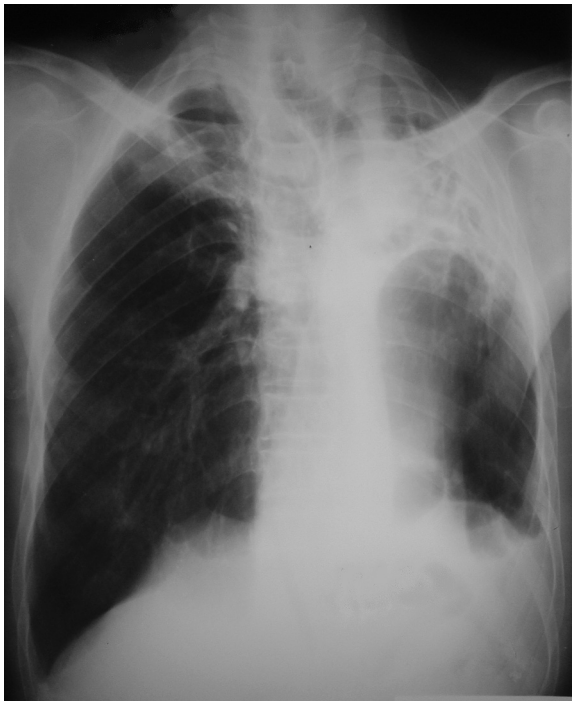

Figure 2 Chest radiograph of severe post-infectious pulmonary sequelae in a Cambodian patient with acute lower respiratory infection, SISEA study, Cambodia, 2007—2010.

The definitions of clinical conditions, diabetes, renal impairment, cardiovascular disease and severity were described elsewhere [6,7]. First-line antibiotherapy was defined as the antibiotics regimen received during the first three days of hospitalization.

Statistical analysis

Median and interquartile range (IQR) were calculated for continuous data. Number and percentages were determined for categorical data. Characteristics of patients with ALRIPS were initially compared to those of patients with ALRIHL and to those of active pulmonary TB cases using either Chi-square, or non-parametric tests (Kruskal—Wallis), as appropriate.

To identify clinical risk factors of having a superinfection on pulmonary sequelae on admission, the following variables with p values <0.2 were then introduced in backward stepwise logistic regression analysis: age in 10-year classes, gender, comorbidities, clinical signs, and severity.

Statistical significance was defined at a 5% threshold ($p < 0.05$). Odd ratios (ORs) are shown only for variables remaining significant within the final model. Analyses were performed using Stata 12® (Stat Corp., College Station, TX, USA) software program.

Results

Demographic, clinical, microbiological and therapeutic characteristics of ALRIPS

Among 2351 patients aged 15 years and above included in the surveillance project, 1831 cases with abnormal chest

radiographs matched the ALRI definition (Fig. 1). Among TB and ALRIPS patients, 20 had sequelae in association with TB and were excluded from analysis (Fig. 1). A total of 1800 patients were finally eligible: 426 ALRIPS (18%), 878 ALRIHL (37%) and 496 TB (n = 21%). Demographic and clinical characteristics of these patients are summarized in Table 1. Of the 426 ALRIPS cases, 47 (11%) reported current or previous tobacco use. More than a half (n = 264, 62%) received treatment prior to admission; only 25 (6%) patients said they had taken antibiotics. While most (n = 372, 87%) of the patients had a productive cough on admission, 68 (16%) had hemoptysis. Chest radiographs showed major sequelae in 367 (86%) patients. Eleven patients (3%) were severe on admission.

In the three groups, blood cultures and sputum samples were obtained for 1649 (92%) and 890 (49%) patients, respectively. The main pathogens identified are presented in Table 2. In the ALRIPS group, *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Pseudomonas aeruginosa* accounted for 91 (83%) of the 109 positive sputum and one blood culture. Of the 51 *H. influenzae* strains with antibiotic susceptibility testing results, 23 (45%) produced a penicillinase, but all of those remained susceptible to amoxicillin-clavulanate. All the isolated strains of *S. pneumoniae* were susceptible to amoxicillin. *P. aeruginosa* presented no resistance, except to ciprofloxacine in two (13%) strains. Concurrent virus detection was noted in 15 (3.5%) patients. Four chest radiographs were highly suggestive of aspergilloma but fungal culture of sputum samples could not be performed.

The first-line antibiotic prescribed in ALRIPS was penicillin A for 283 (66%) patients, in combination with aminoglycosides for 47 (11%). Only 33 (8%) patients received amoxicillin-clavulanate, which was not available at hospital pharmacies, and 15 (3.5%) ceftriaxone. Treatment was correctly adapted to subsequently available antibiotic susceptibility testing results for 198 (61%) patients, including 58% (30/52) of patients with *H. influenzae*, 74% (17/23) with *S. pneumoniae*, none (0/15) with *P. aeruginosa*, and 42% (5/12) with *Klebsiella pneumoniae*. The median duration of treatment was seven days (IQR 5—10 days). The median length of stay at hospital was ten days (IQR 7—14 days). In total, six (1%) patients died in hospital; 350 (82%) went home with or without medical discharge.

According to experts' review, ALRIPS were recognized by local clinicians in 108 (25%) patients, while 56 (13%) were misdiagnosed as TB cases including 29 (52%) who were transferred to another hospital and 8 (9%) to another ward (mainly TB ward).

Table 1 Demographic, clinical characteristics and univariate analysis comparing patients aged ≥15 years with acute lower respiratory infections (ALRI) on pulmonary sequelae (ALRIPS) (reference group), ALRI on previously healthy lungs (ALRIHL) and active pulmonary tuberculosis (TB), SISEA study, Cambodia, 2007—2010.

	ALRIPS	ALRIHL	p	TB	p
	n = 426	n = 878		n = 496	
	n (%)	n (%)		n (%)	
Demographic					
Age in years, median (IQR)	60 (52—70)	55 (42—66)	**<0.001**	52 (40—65)	**<0.001**
Male gender	198 (45.9)	439 (50.0)	0.233	268 (54.0)	**0.022**
Co-morbidities					
At least one co-morbidity	143 (33.6)	402 (45.8)	**<0.001**	178 (35.9)	0.461
Cardiovascular disease	25 (5.9)	151 (17.2)	**<0.001**	19 (3.8)	0.148
Diabetes	42 (9.9)	124 (14.1)	**0.03**	58 (11.7)	0.372
Liver disease	2 (0.5)	9 (1.0)	0.304	6 (1.2)	0.227
Renal impairment	4 (0.9)	8 (0.9)	0.961	3 (0.6)	0.56
Tobacco use	47 (11.0)	89 (10.10)	0.619	67 (13.5)	0.255
Excessive alcohol consumption	71 (16.7)	142 (16.2)	0.821	100 (20.1)	0.173
Clinical characteristics					
Severity	11 (2.6)	83 (9.4)	**<0.001**	22 (4.4)	0.131
Hypoxemia	18 (4.2)	64 (7.3)	**0.03**	21 (4.2)	0.995
Hemoptysis	68 (16.0)	54 (6.1)	**<0.001**	59 (11.9)	0.074
Cough	423 (99.3)	871 (99.2)	0.857	491 (99.0)	0.62
productive cough	372 (87.3)	576 (65.6)	**<0.001**	413 (83.3)	0.084
Fever	185 (43.4)	611 (69.6)	**<0.001**	261 (52.6)	**0.005**
Treated prior to admission	264 (62.0)	416 (47.4)	**<0.001**	290 (58.5)	0.279
Outcome					
Discharged alive	350 (82.2)	600 (68.3)	**<0.001**	156 (31.5)	**<0.001**
Transferred to another ward	70 (16.4)	235 (26.8)	**<0.001**	331 (66.7)	**<0.001**
Died or was discharged for death at home	6 (1.4)	43 (4.9)	**0.002**	9 (1.8)	0.627
Length of hospital stay (days)	10 (7—14)	7 (4—11)	**<0.001**	6 (3—9)	**<0.001**

Results are expressed as n (%), otherwise specified. Significant values ($p < 0.05$) are in bold.

Table 2 Microbiological results and univariate analysis comparing patients with acute lower respiratory infections (ALRI) on pulmonary sequelae (ALRIPS) (reference group), with ALRI on previously healthy lungs (ALRIHL), and with active pulmonary tuberculosis (TB), SISEA study, Cambodia, 2007–2010.

Pathogens	ALRIPS	ALRIHL	*p*	TB	*p*
	n (%)	*n* (%)		*n* (%)	
Bacterial cultures of at least one sputum or blood sample	*n* = 414	*n* = 829		*n* = 478	
H. influenzae	53 (12.8)	45 (5.4)	**<0.001**	21 (4.4)	**<0.001**
S. pneumoniae	23 (5.6)	26 (3.1)	**0.039**	10 (2.1)	**0.006**
P. aeruginosa	15 (3.6)	15 (1.8)	**0.05**	5 (1.0)	**0.01**
K. pneumoniae	12 (2.9)	29 (3.5)	0.57	5 (1.0)	**0.044**
S. aureus	5 (1.2)	3 (0.4)	0.087	3 (0.6)	0.28
B. pseudomallei	1 (0.2)	30 (3.6)	**<0.001**	1 (0.2)	0.91
Other Gram negative bacilli	8 (1.9)[a]	16 (1.9)[b]	0.99	3 (0.6)[c]	0.078
Dual bacterial infection	10 (2.4)	15 (1.8)	0.47	3 (0.6)	**0.02**
Viral RT-PCR	*n* = 417	*n* = 853		*n* = 483	
Rhinovirus	20 (4.8)	40 (4.7)	0.93	19 (3.9)	0.52
Influenza A or B	8 (1.9)	9 (1.0)	0.20	3 (0.6)	0.07
Respiratory syncytial virus	9 (2.1)	15 (1.8)	0.62	8 (1.7)	0.58
Coronavirus	10 (2.4)	16 (1.9)	0.53	1 (0.2)	**0.003**
Other viruses	5 (1)[d]	13 (2)[e]	0.65	3 (1)[f]	0.35
Dual viral infection	2	2	0.46	0	NA

NA: not applicable. Significant values are in bold ($p < 0.05$).
[a] *A. baumannii* ($n = 5$), *E. coli* ($n = 2$), *S. marcescens* ($n = 1$).
[b] *A. baumannii* ($n = 6$), *E. coli* ($n = 9$), *R. pickettii* ($n = 1$).
[c] *A. baumannii* ($n = 1$), *E. coli* ($n = 1$), *P. mirabilis* ($n = 1$).
[d] Parainfluenzae virus ($n = 3$), adenovirus ($n = 1$), human metapneumovirus ($n = 1$).
[e] Parainfluenzae virus ($n = 3$), adenovirus ($n = 2$), human metapneumovirus ($n = 7$), bocavirus ($n = 1$).
[f] Parainfluenzae virus ($n = 1$), adenovirus ($n = 2$).

Comparison of ALRIPS with ALRIHL and TB patients

Results of univariate analysis are shown in Table 1. In comparison with ALRIHL and TB, ALRIPS patients were significantly older, 338 (80%) being aged 50 years and above (Fig. 3), and had less fever (43.4% [*vs.* 69.6%; $p < 0.001$]; [*vs.*52.6%; $p = 0.005$], respectively). They also stayed significantly longer at hospital than both other groups, even though they were more frequently alive at discharge. Bacteria cultures were more often positive in ALRIPS than in both ALRIHL and TB groups (26.6% [*vs.* 18.9%; $p = 0.03$]; [*vs.* 10.5%; $p < 0.001$], respectively). *H. influenzae*, *Pseudomonas areuginosa and K. pneumoniae* were more frequently isolated in samples from patients with ALRIPS than from both other groups (Table 2). There was no significant difference for virus yield between groups.

Results of the multivariate analysis are presented in Table 3. Briefly, the ALRIPS group differed from ALRIHL in terms of: older age (over 50 years); less known cardiovascular disease and diabetes; less fever; more productive cough; more hemoptysis; and less severity on admission. In comparison with TB patients, patients with ALRIPS were 40 years and over, had less fever and more hemoptysis.

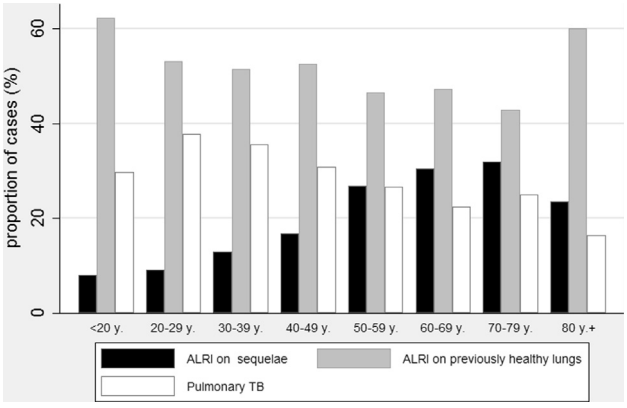

Figure 3 Distribution of acute lower respiratory infections (ALRI) by age group, SISEA study, Cambodia, 2007–2010.

Discussion

Our findings indicate that clinicians and public health specialists are little aware of the burden of unrecognized sequelae in a TB-endemic country. In our study, nearly one in four adult patients admitted for ALRI presented superinfection on post-infectious sequelae. These patients were mostly aged 50 and above. Chronic pulmonary disease was often very advanced and associated with Gram-negative bacilli and *S. pneumoniae*. Although AFB smears remained negative, these cases of superinfected sequelae were misdiagnosed and sometimes treated as active TB. Furthermore, the empiric first-line antibiotic treatment used was inappropriate according to the antibiotic susceptibility testing results in nearly one in three cases.

Table 3 Results of multivariate analysis and odds ratios (OR) of acute lower respiratory infection on previously healthy lungs (ALRIHL) or active pulmonary tuberculosis (TB) groups compared to ALRIPS (reference group), SISEA study, Cambodia, 2007–2010.

Variable	ALRIHL			TB		
	OR	*p*	CI 95%	OR	*p*	CI 95%
Male gender	–	NS	–	NA		
Aged 20–29 years	–	NS	–	–	NS	–
Aged 30–39 years	–	NS	–	–	NS	–
Aged 40–49 years	–	NS	–	1.90	0.013	1.15–3.16
Aged 50–59 years	2.15	<0.001	1.49–3.09	3.52	<0.001	2.21–5.60
Aged 60–69 years	2.45	<0.001	1.72–3.47	4.83	<0.001	3.04–7.69
aged 70–79 years	3.39	<0.001	2.32–4.97	4.69	<0.001	2.91–7.57
Aged ≥ 80 years	3.22	0.003	1.50–6.93	5.56	<0.001	2.18–14.18
Cardiovascular disease	0.35	<0.001	0.22–0.56	–	NS	–
Alcohol abuse	NA			–	NS	–
Diabetes	0.55	0.004	0.36–0.82	NA		
Severity	0.38	0.005	0.19–0.74	–	NS	–
Hypoxemia on admission	–	NS	–	NA		
Fever on admission	0.47	<0.001	0.36–0.61	0.67	0.004	0.51–0.88
Hemoptysis	1.87	0.003	1.23–2.83	1.55	0.031	1.04–2.32
Productive cough	3.16	<0.001	2.26–4.41	–	NS	–
Treatment prior to admission	–	NS	–	NA		

OR: odds ratio; CI 95%: confidence interval 95%; NA: not applicable.

Clinical features were not helpful in distinguishing between active TB, ALRIHL and ALRIPS. Patients in the ALRIPS group had more productive cough and were less often febrile than in the other groups. But taken individually, these symptoms are poor clinical indicators. Hemoptysis was more prevalent in the ALRIPS group compared to both other groups, which is unsurprising due to the frequency of bronchiectasis in post-infectious sequelae. The relatively high proportion of hemoptysis in ALRIHL group may be due to necrotizing bacteria, *K. pneumoniae* or *B. pseudomallei*, which have previously been described by our team, or to smear-negative TB. [6,7]. In Cambodia, smear-negative TB accounted for 20% of the 38 555 TB cases notified in 2011 [14]. Due to limitations of Cambodian laboratory facilities, TB culture is not available. Thus, in our study, smear-negative TB cases would have been missed.

H. influenzae, *S. pneumoniae* and *P. aeruginosa* colonize airways during the course of non-cystic fibrosis bronchiectasis and chronic obstructive pulmonary diseases [15–17]. In the elderly, acute exacerbations of chronic obstructive pulmonary disease, including bronchiectasis exacerbations, are clearly associated with the presence of these bacteria [18]. Our results are consistent with other studies conducted in Thailand and in China, where *P. aeruginosa* and *Haemophilus influenza* were also the two most frequent pathogens in patients with steady-state bronchiectasis [19,20]. *Pseudomonas* colonization of bronchiectasis is associated with forced expired volume decline [20], increased courses of oral antibiotics, increased hospital admissions [21], and subsequent alteration of the quality of life [22]. Unfortunately, spirometric measures are not available in provincial Cambodian hospitals.

This study was not designed to document the epidemiology of mycological and atypical mycobacteria. Fungi such as *Aspergillus* spp. may also colonize bronchiectasis and pre-existingcavities, enhancing hemoptysis when aspergilloma erode bronchial arteries [23]. A short prevalence assessment from the same prospective study performed in 2010 among 138 consecutive patients showed that 21 (15%) were infected with non-tuberculous mycobacteria (i.e *Mycobacterium avium intracellulare*, *M. scrofulaceum*, *M. abscessus*, *M. fortuitum*, *Mycobacterium* spp.) in at least one of three consecutive sputum samples (Institut Pasteur in Cambodia unpublished data). Of these 21 patients, nine presented with ALRIPS. It has been shown that patients with bronchiectasis and post-TB sequelae have a higher risk than other chronic respiratory diseases to develop non-tuberculous mycobacteriosis [24]. Nevertheless, the pathogenicity of atypical mycobacteria is difficult to establish in this study and environmental contaminations cannot be excluded [25]. Clinicians, however, have to be aware of such diseases that could overestimate the TB burden. Developing mycobacteria culture and identification throughout the country could help to address this issue.

The currently first-line empirical antibiotic used for ALRI in Cambodia is penicillin A, which remained active on 74% of *Streptococcus pneumonia* strains found in the ALRIPS group. However, 42% of isolated *H. influenzae* and all *P. aeruginosa* strains were resistant to this antibiotic. Cambodian antibiotics guidelines for ALRI are currently under revision and will be adjusted to the local epidemiology. In theory, amoxicillin-clavulanate, ceftriaxone or cefotaxime, or fluoroquinolones are possible choices for first line therapy. There are, however, two major obstacles to the broad use of fluoroquinolones as first-line empirical treatment in Cambodia. On one hand, ofloxacine and ciprofloxacine are not effective as anti-pneumococcal drugs and 13% of *P. aeruginosa* were resistant to ciprofloxacine in our study. On the other hand,

fluoroquinolones currently remain active in TB. [26]. Generalization of fluoroquinolones use could therefore delay TB diagnosis, and trigger widespread emergence of resistant TB strains [27]. Since the presentation of the ALRIPS patients was less severe on admission, fluoroquinolones could be proposed in this group only as a second-line therapy if the first-line treatment is found to be ineffective upon re-evaluation and after the results of AFB screening.

Hospital stay was longer in the ALRIPS group contributing to direct and indirect cost for patient's family. In addition, the low percentage of mortality in this study may be due to under-reported deaths. Patients frequently died at home just after discharge, as already shown in another Cambodian publication about ALRI patients infected with *K. pneumonia* and in a Vietnamese study in HIV-TB co-infected patients [7,28].

One limitation of the study is that diagnosis was based on only one chest radiograph performed on admission. The SISEA project lacked funding to perform follow-up radiological assessment. Most (86%) of the radiographs in our ALRIPS group showed obvious sequelae, which could have easily been recognized by clinicians. However, chest radiographs have limited sensitivity to detect mild abnormalities, and especially bronchiectasis. Some cases with mild bronchiectasis could have been classified in ALRIHL group. In a Thai study on bronchiectasis, 10% of the patients with bronchiectasis detected by computed tomography (CT) scan had a normal chest radiograph [19]. CT scan would have been a better diagnosis tool than chest radiograph in this case, but unfortunately it is not available in Cambodian provincial hospitals.

Conclusion

In conclusion, clinical misdiagnosis and mismanagement of superinfections on post-infectious pulmonary sequelae are frequent and represent a serious threat to patients, to public health and to healthcare finances in a TB-hyperendemic country such as Cambodia. Improving the detection of chronic bronchitis signs, training clinicians on chest radiograph interpretation, implementing mycobacteria culture in Cambodian's laboratories, and implementing the use of simple spirometric measures could help this diagnosis. Further studies are needed to assess the decline of forced expiratory volume and the reduction of the long-term functional prognosis and quality of life of Cambodian patients, in addition to assess the generating added costs to families and the Cambodian health system.

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Conflict of interest

All authors declared no competing interests for the present work. BR received a travel grant from MSD and Gilead.

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