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Epidemiology of respiratory pathogen carriage in the homeless population within 2 shelters in Marseille, France, 2015-2017: Cross sectional one-day surveys

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Abstract

Objectives. To assess risk factors for respiratory tract infection symptoms and signs in sheltered homeless people in Marseille during the winter season, including pathogen carriage.

Methods. Data on 479 male participants within 2 shelters who completed questionnaires and a total of 950 nasal and pharyngeal samples were collected during the winters of 2015-2017. Respiratory pathogen carriage including 7 viruses and 4 bacteria was assessed by quantitative polymerase chain reaction.

Results. The homeless population was characterized by a majority of individuals of North African origin (300/479, 62.6%) with a relatively high prevalence of chronic homelessness (175/465, 37.6%). We evidenced a high prevalence of respiratory symptoms and signs (168/476, 35.3%), a very high prevalence of bacterial carriage (313/477, 65.6%), especially *Haemophilus influenzae* (280/477, 58.7%) and a lower prevalence of virus carriage (51/473, 10.8%) with human rhinovirus being the most frequent (25/473, 5.3%). Differences were observed between the microbial communities of the nose and throat. Duration of homelessness (OR=1.77, p=0.017), chronic respiratory diseases (OR=5.27, p<0.0001) and visiting countries of origin for migrants (OR=1.68, p=0.035) were identified as independent risk factors for respiratory symptoms and signs. A strong association between virus (OR=2.40, p=0.012) or *Streptococcus pneumoniae* (OR=2.32, p=0.014) carriage and respiratory symptoms and signs was also found.

Conclusions. These findings allowed identifying the individuals at higher risk for contracting respiratory tract infections to better target preventive measures aiming at limiting the transmission of these diseases in this setting.

Introduction

Given their lack of customary and regular access to a conventional dwelling or residence, homeless people reside in the street and/or in shelters. The challenge of poor environmental conditions, poor physical state, smoking habit, alcohol abuse or illicit drug consumption significantly impairs their health status. Behind the frequent association with mental disease and unintentional injuries, homeless people are also predisposed to infectious diseases, especially respiratory infections such as tuberculosis and pneumonia [1]. A high prevalence of chronic respiratory diseases was recorded in the homeless, including bronchitis, asthma and chronic obstructive pulmonary disease [2]. Respiratory diseases are frequently associated with death among homeless individuals [3]. Pulmonary tuberculosis is frequent in the homeless population and has been extensively studied [4, 5].

In Marseille, there are an estimated 1500 homeless individuals including more than 800 sleeping in the street and approximately 600 living temporarily at the 2 main shelters of the city [6]. Infectious diseases are frequent among Marseille's sheltered homeless people, including lice and *Bartonella quintana* infection, hepatitis E and C, *Tropheryma whipplei* infection, skin infections and respiratory tract infections [7]. A 50% rate of respiratory symptoms and signs was observed in this population, in winter 2005 [8]. About 8.7% carried at least one respiratory virus, with rhinovirus being the most frequent when sampled during the winters of 2010-2011 [9]. These preliminary finding demonstrated that respiratory infections might be frequent among sheltered homeless people in Marseille, warranting further investigation.

We described socio-demographic characteristics, underlying chronic medical conditions and addictions, clinical respiratory symptoms and signs, and prevalence of respiratory viruses and bacteria (other than *Mycobacterium tuberculosis*) in the homeless population in 2 shelters of Marseille over the 2015-2017 period of time and investigated potential risk factors.

The main objective of the study was the assessment of risk factors for respiratory tract infection symptoms and signs in sheltered homeless people during the French winter season, including pathogen carriage. We hypothesize that carriage of viral pathogens may be associated with clinical signs and symptoms since it is admitted that the vast majority of respiratory infections in adults are caused by rhinoviruses, coronaviruses and influenza viruses [10]; whereas carriage of bacterial pathogens may not necessarily be associated with clinical signs and symptoms since bacterial microorganisms that are potential aetiological agents of respiratory tract infections are also part of the resident microbiome [11]. The secondary objective was to investigate the possible association between viral-bacterial co-carriage or dual bacterial infections and respiratory symptoms and signs, since the pathogenic role of respiratory viruses in virus-bacteria co-infected patients remains unclear [12] and because interspecies interactions in patients infected with several respiratory bacteria is suspected [13].

Methods

Study population and data collection. Ethical approvals were obtained from the Institutional Review Board and Ethics Committee of Marseille (2010-A01406-33). Cross sectional one-day surveys were organized on February 17, 2015, March 7-10, 2016 and February 6-8, 2017 in 2 shelters (A and B) in Marseille, France, housing 600 homeless persons, for the night only, with a high turnover. Shelter A has a special (day-night) unit with a 35-bed capacity, dedicated to high-risk sedentary homeless people who are characterized by a high level of poverty, poor hygiene, alcoholism and mental illness. Adult homeless people were recruited on a voluntary basis. A medical doctor administrated a standardized questionnaire addressing demographics, chronic medical conditions, chronic respiratory disease (CRDs) status (defined as suffering from one of the following conditions: asthma, chronic obstructive pulmonary disease, occupational lung diseases and pulmonary hypertension), substance abuse, vaccination status,

97 symptoms and signs (cough, expectoration, rhinorrhea, dyspnea, sore throat, sibilants, rhonchi,
98 crackles, headache, myalgia, conjunctivitis, fever) at enrollment and physically examined the
99 participants. All patients signed an informed consent. The homeless people screened were
100 offered treatment or further evaluation based on the symptom assessment, since qPCR data
101 were obtained long after the surveys were done.

102 **Respiratory specimens.** Nasal and pharyngeal swabs were collected from each participant,
103 transferred to Sigma-Virocult® medium and stored at -80°C. The DNA and RNA extractions
104 were concurrently performed using the EZ1 Advanced XL (Qiagen, German) with the Virus
105 Mini Kit v2.0 (Qiagen) according to the manufacturer's recommendation. All quantitative
106 real-time PCR (qPCR) reactions were performed using a C1000 Touch™ Thermal Cycle
107 (Bio-Rad, USA). Negative control (PCR mix + sterilized water) and positive control (DNA
108 from bacterial strain or RNA from viral strain) were included in each run. Positive results of
109 bacteria or virus amplification were defined as those with a cycle threshold (CT) value ≤35.
110 Patients having at least one nasal or pharyngeal positive sample were considered positive
111 cases.

112 **Identification of respiratory bacteria.** Real-time PCR amplifications were carried out by
113 using LightCycler® 480 Probes Master kit (Roche diagnostics, France) according to the
114 manufacturer's recommendations. The *SHD* gene of *Haemophilus influenzae*, *phoE* gene of
115 *Klebsiella pneumoniae*, *NucA* gene of *Staphylococcus aureus*, and *lytA* gene of *Streptococcus*
116 *pneumoniae* were detected with internal controls T4 phage as previously described [14, 15]
117 **Identification of respiratory viruses:** One-step duplex qRT-PCR amplifications by
118 HCoV/HPIV-R Gene Kit (REF: 71-045, Biomerieux®, France) were used for the detection of
119 human coronavirus (HCoV) and human para-influenzavirus (HPIV), according to the
120 manufacturer's recommendations. One-step simplex real-time qRT-PCR amplifications were
121 performed by using Multiplex RNA Virus Master Kit (Roche diagnostics, France) for

influenza A (FLUA), influenza B (FLUB), human rhinovirus (HRV), human metapneumovirus (HMPV), human respiratory syncytial virus (HRSV) and internal controls MS2 phage [14]. HCoV positive samples were further screened for HCoV-HKU1, HCoV-NL63, HCoV-229E, and HCoV-OC43 [16].

Statistical analysis

Statistical analysis was conducted using STATA software (version 11.1). Differences in the proportions (percentages and odds ratio (OR) with 95% confidence interval (CI) estimations) were tested by Pearson's chi-square or Fisher's exact tests when appropriate. Two-tailed tests were used for comparisons. Univariate analysis was used to examine unadjusted associations between multiple factors (demographic, chronic medical condition), respiratory symptoms or physical finding and prevalence of respiratory pathogen carriages. A p value <0.05 was considered statistically significant. Only the variables with a prevalence $\geq$ 5.0% were considered for statistical analysis. Variables with p values of <0.2 from the univariate analysis were included in the multivariate analysis. Analysis of multicollinearity among the independent variables was performed using the phi coefficient to test for correlation among binary variables; and for pairs of variables that were highly correlated (Absolute value of correlation coefficient >0.7), only one variable was entered into the multivariate model. Multivariable logistic regression (created by step-wise regression) was used to determine factors associated with respiratory symptoms and signs. Log likelihood Ratio Tests were performed to determine these multivariable modeling.

Results

Since only 2 women were identified, they were excluded. Of the 479 male individuals who answered the questionnaire and signed consent forms, 477 patients agreed to undergo nasal or pharyngeal sampling. About 11550 qPCR reactions were performed.

Characteristics and clinical status of the homeless participants

The socio-demographic characteristics, substance abuse, chronic disease and clinical features of participants are shown in Table 1 and Figure 1. The population was characterized by middle-aged males (43.6 ± 16 years old) of North African origin, with a relatively high proportion of chronic homelessness (more than one year) reported by 37.2% of individuals and with a 61.2% prevalence of tobacco smoking. About 8% reported suffering from CRDs. The prevalence rate of at least one respiratory symptom or sign was of 35.3% with cough, rhinorrhea and dyspnea as the most frequent symptoms. Most symptomatic individuals (70.8%, 119 out of 168) were smoking tobacco or suffering from CRDs.

Prevalence of respiratory pathogens by real-time PCR

We evidenced a high prevalence of respiratory carriage of bacteria (65.6%, 313 of 477), notably, the proportion of individuals colonized by *H. influenzae* in nasal and/or pharyngeal swabs was of 58.7% (n=280) and that of *S. pneumoniae* was of 12.4% (n=59). Fifty-one patients (10.8%) were also tested positive for at least one virus by qRT-PCR. When comparing nasal and pharyngeal sampling sites, we found that *H. influenzae* was significantly more frequently detected in pharyngeal samples compared to nasal samples, while the prevalence of *S. aureus* and HRV in nasal samples was significantly higher than in pharyngeal samples (shown in Table 2). Co-infections were frequently observed with the most frequent being *H. influenzae*-virus and *H. influenzae-S. pneumoniae* co-infections (Table 1).

Association between demographics, chronic medical conditions, respiratory pathogen carriage and clinical findings according to respiratory symptoms and signs in univariate analysis and multivariate analysis

Respiratory symptom and signs prevalence significantly increased with the duration of homelessness (Table 1). The prevalence of symptoms and signs was higher in individuals ≥ 50 years of age, suffering from chronic respiratory diseases and in individuals born in France but

was lower in individuals born in Sub-Saharan Africa. Among migrants, the symptom and sign prevalence was significantly higher in those visiting their country of origin compared to others. Individuals carrying at least one virus, *S. pneumoniae* or *H. influenzae-S. pneumoniae* co-infection were more likely to present with at least one respiratory symptom or sign. In the multivariate analysis, only individuals experiencing chronic homelessness (OR=1.77 [1.11-2.83], p=0.017), those visiting their country of origin (OR=1.68 [1.04-2.71], p=0.035), those suffering from chronic respiratory diseases (OR=5.27 [2.24-12.41], p<0.0001), and those carrying at least one virus (OR=2.40 [1.21-4.74], p=0.012) or *S. pneumoniae* (OR=2.32 [1.18-5.3], p=0.014) remained associated with an increased prevalence of respiratory symptoms and signs (Table 3). Overall, individuals carrying at least one virus were more likely to present with cough, expectoration, rhinorrhea and sore throat. Carriage of *S. pneumoniae* was associated with cough (Table 4).

Discussion

The sheltered homeless population in our study was characterized by a high proportion of migrants of North African origin with a high prevalence of smoking habits and CRDs. We observed a high prevalence of respiratory symptoms and signs (35%) in line with the results of a survey conducted in Italy and The Netherlands [17, 18]. Dry or productive cough, rhinorrhea and dyspnea were the symptoms most frequently observed, suggesting that both upper and lower tract respiratory infections affect a significant proportion of sheltered homeless people during winter. We found relatively low rates of influenza virus infections. Cross sectional surveys took place when influenza was epidemic in the region of Marseille. Influenza vaccination rate in the homeless population screened in our surveys was in the same range in Marseille's overall population [19, 20]. This result may indicate that the social isolation of homeless people might have a protective impact against community influenza virus transmission. One of the most important findings of this study is the very high prevalence of

198 bacterial colonization by respiratory bacteria with *H. influenzae* (59%), and *S. pneumoniae*
199 (13%), which were the most frequent. A high prevalence of *H. influenzae* carriage (70%) was
200 also observed by direct PCR, in healthy infants from the Western region of Gambia [21] and a
201 rate of 40.9% was reported among children aged ≤6 years in day-care centers in eastern France
202 [22]. In surveys conducted among healthy adults in the Australian Aboriginal population, the
203 prevalence of non-typeable *H. influenzae* reached approximately 22.9% when culturing
204 nasopharyngeal samples [23]. A 2.3% *H. influenzae* nasal prevalence was observed in
205 Marseille's individuals originating from North-Africa by qPCR in 2013 [17], however, the
206 survey was conducted in October, which may account for a lower prevalence, as shown in
207 another healthy Italian children population [24]. *K. pneumoniae* naso-pharyngeal carriage rates
208 have been reported to range from 3 to 15%, which is in agreement with our results [25]. This
209 bacterium is known to be frequently multidrug-resistant [25] and further studies on drug
210 resistance in bacteria isolated from homeless people would be of interest.

211 We identified chronic homelessness, chronic respiratory diseases and visiting countries of
212 origin for migrants as independent risk factors for respiratory symptoms and signs. We
213 found a strong association between virus or *S. pneumoniae* carriage and respiratory symptoms
214 and signs, reinforcing the need to increase vaccination rates in this population.
215 Additionally, data obtained in this study emphasizes the difference between the microbial
216 communities of the nose and throat, indicating the need for both nasal and pharyngeal swabs
217 sampling in future studies to better assess upper respiratory microbiological carriage.

218 Our study has several limitations. The first is that we did not use a control group for
219 evaluation of background carriage in the healthy adult population. The second limitation is
220 that our survey took place in winter, so we could not have an overview about seasonal
221 variations of carriage in the homeless, whereas it was demonstrated to have impacted the
222 airway microbial community in adults and children [24, 26]. Future studies will be conducted

at least twice a year (in winter and in summer). The questionnaire design did not allow a clear distinction between acute (short-term) and chronic (going on) respiratory symptoms which needs to be considered in further studies. Finally, the level of precariousness of the homeless was limited to the duration of homelessness and more detailed information should be recorded in future studies.

In summary, we confirm the high prevalence of respiratory symptoms and signs in sheltered homeless people associated with a high level of bacterial carriage in the respiratory tract. Several risk factors for respiratory symptoms and signs were identified, allowing a better identification of individuals at higher risk on whom to base targeted preventive interventions, including notably vaccination against influenza and *S. pneumoniae* infections. Such an approach has proven effective in identifying individuals at higher risk for body lice in the same population [27] and the results of our study will benefit to homeless people in the future.

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Potential conflicts of interest

No reported conflicts of interest.

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320 **Table 1. Risk factors for respiratory disease: univariate analysis**

Characteristics	Total (N)	At least one respiratory symptom or sign N (%)	No respiratory symptom and no sign N (%)	Univariate analysis Odds ratio (95%CI), p-value
Total		**168 (35.3)**	**308(64.3)**	
Year of study*				
2015	125 (26.1)	37 (29.6)	88 (70.4)	
2016	156 (32.6)	74 (47.4)	82 (52.6)	
2017	198 (41.3)	57 (29.2)	138 (70.8)	
Shelter				
A	311 (64.9)	107 (35.2)	201 (65.3)	0.93 [0.63-1.38], p=0.73
B	168 (35.1)	61 (36.3)	107 (63.7)	Ref
Age				
Mean age (SD)	43.6±16 years	NA		
Age range	18-84 years	NA		
≤50 years of age	318 (66.8)	98 (30.8)	220 (69.2)	Ref
>50 years of age	158 (33.2)	69 (44.2)	87 (55.8)	1.78 [1.20-2.64], p=0.004
Birthplace				
France (mainland)	71 (14.8)	39 (54.9)	32 (45.1)	Ref
France (overseas territories)	1 (0.2)	0 (0)	1 (100)	NA
North Africa	300 (62.6)	100 (33.4)	199 (66.6)	0.41 [0.25-0.70], p=0.001
Sub-Saharan Africa	43 (9.0)	7 (16.3)	36 (83.7)	0.16 [0.63-0.41], p<0.0001
East Europe	35 (7.3)	13 (39.4)	20 (60.6)	0.53 [0.23-1.24], p=0.14
West Europe	9 (1.9)	2 (22.2)	7 (77.8)	0.23 [0.04-1.21], p=0.08
Asia	20 (4.2)	7 (35.0)	13 (65.0)	0.44 [0.16-1.24], p=0.12
Other	0 (0)			NA
Mean duration of residence in France (SD)	9.88 (0-25.4)	NA	NA	
Range of duration of residence in France	0-65 years	NA	NA	
≥ 1 year	220 (55.3)	79 (35.9)	141 (64.1)	1.52 [0.99-2.32], p=0.06
< 1 year	178 (44.7)	48 (27.0)	130 (73.0)	Ref
Visit to country of origin since immigration	126 (31.9)	51 (40.5)	75 (59.5)	1.76 [1.13-2.74], p=0.012
No visits to country of origin since immigration	269 (68.1)	75 (27.9)	194 (72.1)	Ref
Mean duration of homelessness (SD)	2.66 years (0-7.8)	NA	NA	
Range of duration of homelessness	0-52 years			

≥ 1 year	175 (37.6)	80 (45.7)	95 (70.6)	2.02 [1.37-2.99], p<0.0001
<1 year	290 (62.4)	85 (29.4)	204 (70.6)	Ref
Addiction				
Alcohol				
Frequent	52 (10.9)	24 (47.1)	27 (52.9)	1.75 [0.98-3.14], p=0.06
Rare or never	424 (89.1)	143 (33.7)	281 (66.3)	Ref
Tobacco				
Yes	293 (61.2)	113 (38.7)	179 (61.3)	1.48 [1.00-2.20], p=0.05
Never	185 (38.7)	55 (30.3)	129 (70.1)	Ref
Cannabis	75 (15.7)	28 (37.3)	47 (62.7)	1.11 [0.67-1.85], p=0.69
Injected substances	2 (0.4)	0 (0)	2 (100)	
Snorted substances	13 (2.7)	4 (30.8)	9 (66.2)	
Drug substitutes	1 (0.2)	1(100)	0 (0)	
Chronic diseases				
Chronic respiratory diseases	38 (8.1)	27 (71.0)	11 (28.9)	5.12 [2.47-10.62], p<0.0001
Diabetes mellitus	36 (7.6)	14 (38.9)	22 (61.1)	1.18 [0.59-2.37], p=0.65
Cancer	5 (1.1)	1 (20)	4 (80)	
Hepatitis	10 (2.1)	8 (80)	2 (20)	
Body mass index				
Mean body mass index	24.4 ± 4.0 (kg/m2)	NA	NA	
Range of Body mass index				
Normal weight	251 (55.9)	86 (34.3)	165 (65.7)	Ref
Underweight	17 (3.8)	9 (52.9)	8 (47.1)	0.46 [0.17-0.24], p=0.12
Overweight	138 (30.7)	47 (34.1)	91 (65.9)	1.00 [0.65-1.56], p=0.97
Obesity	43 (9.6)	12 (27.9)	31 (72.1)	1.35 [0.65-2.75], p=0.41
Seasonal vaccination against influenza	71 (15.1)	31 (43.7)	40 (56.3)	1.50 [0.90-2.5], p=0.12
Respiratory carriage				
Haemophilus influenzae	280 (59.6)	90 (32.4)	189 (67.7)	0.73 [0.50-1.08], p=0.11
Streptococcus pneumoniae	59 (12.4)	32 (54.2)	27 (45.8)	2.45 [1.42-4.29], p= 0.001
Staphylococcus aureus	35 (7.3)	10 (26.8)	25 (71.4)	0.72 [0.33-1.53], p=0.4
Klebsiella pneumoniae	35 (7.3)	11 (31.4)	24 (68.6)	0.83 [0.40-1.75], p=0.63
At least one virus	51 (10.8)	26 (51)	25 (49)	2.09 [1.17-3.49], p=0.012
Human rhinovirus	25 (5.3)	11 (44)	14 (56)	1.48 [0.65-3.34], p=0.34
Human coronavirus	10 (2.1)	5 (50)	5 (50)	
Influenza A	7 (1.5)	4 (57.1)	3 (42.9)	
Influenza B	7 (1.5)	5 (71.4)	2 (28.6)	

Human respiratory syncytial virus	3(0.6)	1(33.3)	2 (66.6)	
Human para-influenza virus	1(0.2)	1(100)	0	
Human metapneumovirus	0	0	0	
Co-infection				
H. influenzae + *S. pneumoniae*	43 (9.0)	24 (55.8)	19 (44.2)	2.55 [1.35-4.82], p=0.003
H. influenzae + *virus*	33 (7.0)	14 (42.2)	19 (57.6)	1.4 [0.68-2.85], p=0.36
H. influenzae +*K. pneumoniae*	25 (5.2)	6 (24)	19 (76)	0.57 [0.22-1.45], p=0.23
H. influenzae + *S. aureus*	24 (5.0)	8 (33.3)	16 (66.7)	0.92 [0.38-2.19], p=0.85
S. pneumoniae + *virus*	12(2.5)	9 (75)	3 (25)	
S. pneumoniae + *S. aureus*	9 (1.9)	4(44.4)	5(55.6)	
S. pneumoniae + *K. pneumoniae*	5 (1.0)	3 (60)	2 (40)	
S. aureus+ *K. pneumoniae*	4 (0.8)	0	4(100)	
S. aureus+ *virus*	4 (0.8)	3 (75)	1 (25)	

321 Abbreviations: SD, standard deviation; NA, not applicable, Ref, Reference category

322 * Year of study was not included in the analysis, given that no intervention could be done based on this criterion.

323

Table 2. Prevalence (%) of bacteria and viruses detected by qPCR

Respiratory pathogen	Positive carriage			
	Nasal specimen, N (%)	Pharyngeal specimen, N (%)	p-value	Nasal or pharyngeal, N (%)
Total	**476 (100)***	**474 (100)***		**477 (100)***
Bacteria	**105 (22.1)**	**280 (59.1)**	**<0.0001**	**313 (65.6)**
Haemophilus influenzae	46 (9.8)	266 (56.4)	<0.0001	280 (58.7)
Klebsiella pneumoniae	17 (3.5)	20 (4.2)	0.61	35 (7.3)
Staphylococcus aureus	28 (5.9)	12 (2.5)	<0.001	35 (7.3)
Streptococcus pneumoniae	33 (7.0)	36 (7.6)	0.69	59 (12.4)
Virus	**34 (7.1)**	**24 (5.1)**	**0.18**	**51 (10.8)**
Influenza A	4 (0.8)	4 (1.0)	-	7 (1.5)
Influenza B	4 (0.8)	6 (1.3)	-	7 (1.5)
Human rhinovirus	20 (4.3)	7 (1.5)	<0.001	25 (5.3)
Human respiratory syncytial virus	1 (0.2)	2 (0.4)	-	3 (0.6)
Human metapneumovirus	0 (0)	0 (0)	-	0 (0)
Human coronavirus	5 (1.1)	5 (1.1)	0.99	10 (2.1)
HCoV-HKU1	0 (0)	1 (0.2)	-	1 (0.2)
HCoV-E229	3 (0.6)	1 (0.2)	-	4 (0.8)
HCoV-NL63	1 (0.2)	0 (0)	-	1 (0.2)
HCoV-OC43	1 (0.2)	3 (0.6)	-	4 (0.8)
Human para-influenza virus	0 (0)	1 (0.2)	-	1 (0.2)

*473 patients had both nasal and pharyngeal sampling; 3 patients had only nasal swabs and 1 patient had only pharyngeal swabs. Patients having at least one nasal or pharyngeal positive sample were considered positive cases.

328 **Table 3. Risk factors for respiratory disease: multivariate analysis**

Characteristics*	Multivariate analysis Odds ratio (95%CI), p-value
Age ≥ 50 years vs others	-
Birthplace	-
Range of duration of residence in France ≥ 1 year vs others	-
Visit to country of origin since immigration	**1.68 [1.04-2.71], p=0.035**
Range of duration of homelessness ≥ 1 year vs others	**1.77 [1.11-2.83], p=0.017**
Alcohol	-
Tobacco	-
Chronic respiratory diseases	**5.27 [2.24-12.41], p<0.0001**
Seasonal vaccination against influenza	-
Respiratory pathogen	
Haemophilus influenzae	-
Streptococcus pneumoniae	**2.32 [1.18-5.3], p=0.014**
At least one virus	**2.40 [1.21-4.74], p=0.012**
H. influenzae + *S. pneumoniae* co-infection	-

329 Abbreviations: vs, versus

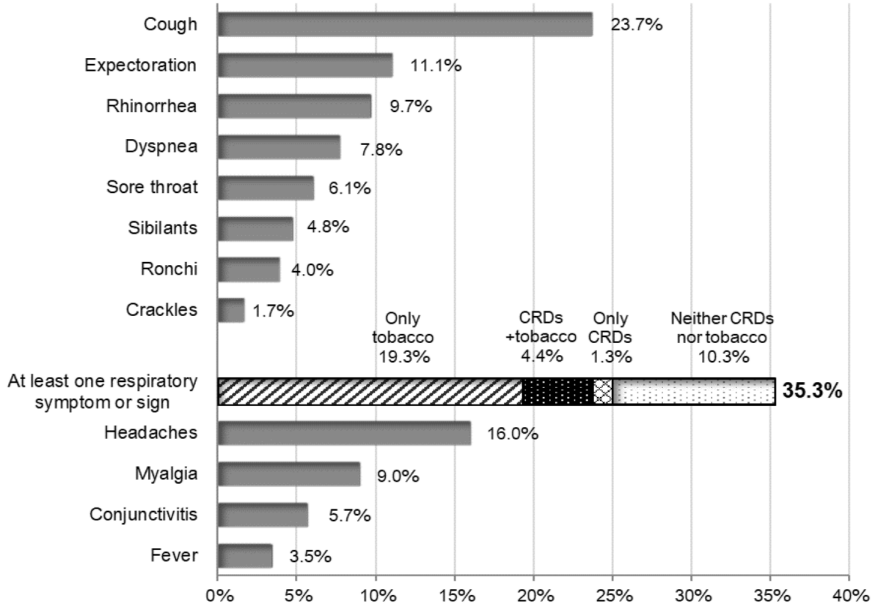
330 ***** Only variables with p values of <0.2 in the univariate analysis and with a paired correlation coefficient < 0.7 were included in
331 the multivariate analysis.

Table 4. Association between respiratory pathogen carriage and clinical findings in univariate analysis according to respiratory symptoms and signs

Respiratory pathogen	Odds ratio (95%CI), p-value				
	Cough	Expectoration[a]	Rhinorrhea[a]	Dyspnea	Sore throat
Streptococcus pneumoniae	**2.5 [1.41-4.41], p=0.001**	1.3 [0.59-2.95], p=0.51	1.03 [0.3-3.59] p=0.965	1.10 [0.41-2.95] p=0.85	1.13 [0.38-3.37], p=0.83
At least one virus	**2.5 [1.37-4.58], p=0.002**	**2.15 [1.01-4.60] p=0.044**	**2.5 [1.00-6.12], p=0.047**	1.68 [0.66-4.24], p=0.27	**7.3 [3.26-16.42], p<0.0001**

335 **Figure 1. Prevalence of clinical signs and symptoms over the 2015-2017 period (N=479**
336 **individuals).**

337 Abbreviations: CRDs, chronic respiratory diseases.


Cough
23.7%
Expectoration
11.1%
Rhinorrhea
9.7%
Dyspnea
7.8%
Sore throat
6.1%
Sibilants
4.8%
Ronchi
4.0%
Crackles
1.7%
Only tobacco 19.3%
CRDs +tobacco 4.4%
Only CRDs 1.3%
Neither CRDs nor tobacco 10.3%
At least one respiratory symptom or sign
35.3%
Headaches
16.0%
Myalgia
9.0%
Conjunctivitis
5.7%
Fever
3.5%
0%
5%
10%
15%
20%
25%
30%
35%
40%