Accepted Manuscript

British Journal of General Practice

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Verheij, Theo; Cianci, Daniela; van der Velden, Alike; Butler, Christopher; Bongard, Emily; Coenen, Samuel; Colliers, Annelies; Francis, Nick; Little, Paul; Godycki-Cwirko , Maciek; Llor, Carl; Chlabicz, Slawomir; Lionis, Christos; Sundvall, Pär-Daniel; Bjerrum, Lars; De Sutter, An; Aabenhus, Rune; Jonassen Harbin, Nicolay; Lindbaek, Morten; Glinz, Dominik; Bucher, Heiner; Kovacs, Bernadett; Seifert, Bohumil; Touboul Lundgren, Pia; de Paor, Muireann; Radzeviciene JUrgute, Ruta; Matheeussen, Veerle; Goossens, Herman; Ieven, Margareta

DOI: https://doi.org/10.3399/BJGP.2021.0344

To access the most recent version of this article, please click the DOI URL in the line above.

Received 09 June 2021
Revised 27 September 2021
Accepted 04 October 2021

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Abstract

Background

There is little evidence about the relation between aetiology, illness severity and clinical course of respiratory tract infections (RTI) in primary care. Understanding these associations would aid to develop effective management strategies for these infections.

Aim

To investigate whether the clinical presentation and illness course differ between RTI in whom a viral pathogen was detected and those in whom a potential bacterial pathogen was found.

Design and setting

Post hoc analysis of data from a pragmatic randomised trial on the effects of oseltamivir in patients with influenza-like illness (ILI) in primary care (n=3266) in 15 European countries.

Methods

Patient characteristics, signs and symptoms were registered at baseline. Naso-pharyngeal (adults) or nasal and pharyngeal (children) swabs were taken for PCR analysis. Patients were followed up until 28 days after inclusion. Regression models and Kaplan-Meier curves were used to analyse the relation between aetiology, clinical presentation at baseline and course of disease including complications.

Results

Except for a less prominent congested nose (OR 0.55, CI 0.35 – 0.86) and acute cough (OR 0.52, CI 0.27 – 0.65) in ILI patients in whom a possible bacterial pathogen was isolated, there were no clear clinical differences in presentations between those with a possible bacterial aetiology than in those with a viral one. Also the course of disease and complications were not related to aetiology.

Conclusion

Given the currently available microbiological tests and antimicrobial treatments, and outside pandemics like COVID-19, microbiological testing in primary care patients with ILI seems to have limited value.

How this fits in

Both GPs and patients still assume that a distinction between viral and bacterial infections is important for illness prognosis and treatment decisions. In this paper illness severity and course of disease in patients with influenza-like illness (ILI) was linked to the presence of viral and bacterial pathogens. The results show that there were no meaningful differences in illness severity at presentation and course of disease between patients in whom viral, bacterial or mixed pathogens were found. Outside specific circumstances like the current COVID-19 pandemic, distinction between viral and bacterial respiratory infections in patients with ILI does not seem clinically relevant.

Introduction

Evidence-based antibiotic use reduces an important driver of antimicrobial resistance and unnecessary exposure to side-effects, and leads to better resource utilisation. In primary care unnecessary antibiotic use is common, especially for patients with respiratory tract infections (RTI).(1)(2) It is commonly assumed that distinguishing viral from bacterial pathogens will lead to only those patients with a potential bacterial pathogen being considered for treatment, as those with a viral aetiology are unlikely to receive benefit from antibiotic therapy. The need for point of care tests to distinguish between bacterial and viral infections in primary care is therefore felt by many and the focus of several studies.(3)(4)(5) However, there is a paucity of evidence about the relationship between aetiology, illness severity and clinical course of RTI in primary care. In a study of lower RTI in primary care, we found that discoloured sputum was the only feature independently related to isolation of a probable bacterial pathogen, but this weak association had limited clinical utility.(6) Furthermore, we compared the illness course of adult primary care patients with an identified potential bacterial pathogen with the illness course of those in whom no bacterial pathogen was detected and found no difference in duration of symptoms, although we did find that those with a potential bacterial identified had slightly more severe symptoms at day 2 to 4.(7) However, we did not compare the illness course in those with a viral aetiology to those with a potential bacterial pathogen, and to those with a potentially dual (viral and bacterial) aetiology, and this study was limited to adults with lower RTI. Thus, it is important to study the relation between presentation and course of disease and microbiological aetiology, to support the development of relevant diagnostic and therapeutic strategies of common RTI in primary care. We therefore compared the clinical presentation and illness course in patients with ILI in whom a viral, a bacterial, and a dual infection was identified.

Methods

Data used in this analysis were collected during an open-label, pragmatic, adaptive, randomised controlled trial on the additional effects of oseltamivir to usual care (symptomatic treatment and/or wait and see in almost all subjects) in patients aged one year and older presenting with influenza-like illness in primary care. Influenza-like illness was defined as a sudden onset of self-reported fever, with at least one respiratory symptom (cough, sore throat, or running or congested nose) and one systemic symptom (headache, muscle ache, sweats or chills, or tiredness), with symptom duration of 72 hours or less during a seasonal influenza epidemic. The primary endpoint of the trial was time to recovery, defined as return to usual activities, with fever, headache, and muscle ache minor or absent.(8) Between Jan 15, 2016, and April 12, 2018, we recruited 3266 participants in 15 European countries during three seasonal influenza seasons, allocated 1629 to usual care plus oseltamivir and 1637 to usual care, and ascertained the primary outcome in 1533 (94%) and 1526 (93%) respectively. (9) A baseline case report form was completed covering overall clinician-rated severity of influenza-like illness (general practitioners' global impression of mild, moderate, or severe illness without provided, predefined criteria), duration of symptoms, comorbidity, temperature, pulse, individual symptom severity rating (patient-reported at inclusion), and usual care advice (registered by general practitioner). Oropharyngeal and nasal flocked swabs (COPAN, Brescia, Italy) were taken from participants younger than 16 years of age and flocked naso- pharyngeal swabs (COPAN, Brescia, Italy) from those aged 16 years or older. Clinicians were trained in swabbing techniques using face-to-face and online video methods. The Fast Track Diagnostics Respiratory Pathogens 21 plus real-time PCR assay (Fast Track Diagnostics, Luxembourg) was used for the qualitative

detection of influenza A, influenza B, influenza A H1N1, human coronaviruses NL63, 229E, OC43 and HKU1, parainfluenza viruses 1, 2, 3 and 4, human metapneumovirus A and B, rhinovirus, respiratory syncytial viruses A and B, adenovirus, enterovirus, parechovirus, bocavirus, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Streptococcus pneumoniae*, *Haemophilus influenzae* B and *Staphylococcus aureus*." , but results were not available for clinicians nor for patients to influence management. Patients were asked to complete a symptom diary for 14 days to indicate when they had returned to their usual daily activities and to evaluate fever, running or congested nose, sore throat, headache, cough, shortness of breath (adults only), muscle ache, sweats or chills (adults only), diarrhoea, nausea or vomiting, abdominal pain, low energy or tired, not sleeping well, dizziness, and feeling generally unwell. Symptoms were scored as either no, minor, moderate, or major problem. For children aged 12 years and younger, the diaries were supplemented with child-specific questions from the Canadian Acute Respiratory Illness Flu Scale . Patients were contacted by telephone between days 2 and 4, days 14 and 28, and after 28 days to support study participation and diary completion, monitor intervention adherence, and ascertain a minimal outcome dataset.

Data analysis

Baseline characteristics were summarized as patient counts and percentages. Symptom severity was dichotomized in major and moderate vs minor and no problem. A variable that indicates the viral aetiology (with or without a bacterial pathogen) was created as follow: 'negative' indicates that no viruses nor bacteria were observed; 'viral' indicates that at least one virus was observed but no bacteria; 'mixed' indicates that in the sample at least one virus and at least one bacterium were present; 'bacterial' indicates no viruses were observed but at least one bacterium.

In order to investigate whether viral and/or a possible bacterial aetiology had a relationship with the severity of each symptom, logistic regression models were used. We use the term possible bacterial aetiology because we realise that in a minority of patients bacterial carriership should be considered. The investigated symptoms were fever, nasal congestion or runny nose, sore throat, cough, diarrhoea, headache, muscle aches and / or pains, low energy or tiredness, not sleeping well and their severity (major and moderate vs minor and no problem). A model for each symptom was run and the variables included in the model were the 4 combinations of presence and absence of viral and/or bacterial pathogen, age categorized as adults (≥12 years) and children (<12 years) and duration of ILI symptoms at baseline (measured as 1, 2 or 3 days). Results are expressed in terms of odds ratios, where 1 indicates that the viral / bacterial pathogen does not affect the outcome, OR>1 indicates that a specific viral / bacterial pathogen is associated with higher odds of outcome and OR<1 indicates that a specific viral / bacterial pathogen is associated with lower odds of outcome. In this analysis we focused on differences between viral and possible bacterial infections and chose the largest category 'viral' as reference category .

The time to resumption of usual activities with fever, headache and muscle ache being a minor or no problem was visualized with Kaplan-Meier curves for the 4 combinations of presence and absence of viral and/or bacterial pathogen. In addition, using the same outcome, a Cox model was generated including age group, treatment group (usual care plus oseltamivir and usual care only), the presence of comorbidities such as diabetes and chronic respiratory conditions, use of pain medications (defined as use of paracetamol, ibuprofen or other pain medication, at least 2 doses in 1 day) or antibiotics and duration of ILI symptoms (measured as 1, 2 or 3 days). Kaplan-Meier curves were also produced for the outcome resolution to

minor or no problem of all the following symptoms: fever, nasal congestion or runny nose, sore throat, headache, cough, muscle aches and / or pains, diarrhoea, low energy or tiredness, not sleeping well, being all minor or no problem.
It was also descriptively investigated whether clinically relevant complications were related to microbiology results.
The statistical analyses were performed with SAS Enterprise Guide (version 8.2).

Results

3266 participants were included in the original trial described above. No pathogens, only a viral pathogen, only a bacterial pathogen, and both viral and bacterial pathogens were found in 849 (26.3%), 1949 (60.4%), 90 (2.8%) and 339 (10.5%) patients respectively (Table 1). See also table S2 for an inventory of the different bacteria and viruses found. Therefore, 2288 (70.9%) patients had a viral pathogen detected and 429 (13.3%) had a bacterial pathogen detected. The majority of patients had a typical flu-like illness with fever, runny nose and acute cough, together with fatigue and muscle ache.

-table 1-

At baseline we observed that patients in whom only bacterial pathogen was seen or no virus/bacteria was found, had somewhat less severe nasal congestion, and cough than those in whom only a viral aetiology was seen. Patients with a longer previous duration of symptoms had a more serious acute cough. No relevant difference was observed for the other symptoms. Irrespective of which pathogen was found, children and adults showed some differences at baseline, but without a clear consistent pattern. (Table 2) In patients over 75 years of age the results did not differ significantly from those in adults. (data not shown)

-table 2-

Time to resume usual activities with fever, headache and muscle ache being a minor or no problem did not differ significantly between patients, irrespective of whether a viral or bacterial pathogen or mixed infection was detected (Figure 1). These results did not change after adjusting for age, treatment group, co-morbidities, medication taken and duration of ILI symptoms at baseline (Supplementary table 1). When we examined resolution of all symptoms, we found no differences between the different groups with presence/absence of viruses and/or bacteria (Supplementary figure 1).

-figure 1-

Clinically relevant complications like need for hospital admission were relatively few (64 patients) and did not seem to be related to microbiology results in study participants.

Discussion

Summary

Except for a somewhat less prominent congested nose and acute cough in ILI patients in whom a possible bacterial pathogen was isolated there were no clear clinical differences in presentations between those with a possible bacterial aetiology than in those with a viral one. Also course of disease and complications were not related to aetiology identified by microbiology test results.

Strengths and limitations

Strengths of our post hoc analysis is the sample size, the participation of a wide range of European countries and real-time PCR tests of naso-pharyngeal swabs taken in all adult patients (nasal and oropharyngeal swabs in children) Also some limitations must be taken into account when assessing our study results. First, study participants had flu-like illness, and very few of these had signs of pneumonia on clinical examination. Nevertheless, our results are generalizable to a large proportion of patients seen each winter season in primary care. Second, the study participants were included during influenza seasons only, and therefore it could be that the proportion of viral infections could differ from respiratory infections outside flu seasons. However, in studies in community-acquired respiratory infections outside influenza epidemics, viral infections are also far more common than bacterial infections. (10)(11) Third, some specific viral and/bacterial infections could have specific presentation and course of disease. Vos et al showed that common viruses other than influenza account for a similar disease burden to influenza infection. (12) However, the current COVID pandemic showed that new pathogens surely can have a specific morbidity and mortality and testing for those new pathogens can of course be relevant. Fourth, both bacterial and viral strains that were identified could reflect asymptomatic carriage, and be unrelated to the signs and symptoms of the patient. This limitation is more important in children than in adults. In recent studies in adults, the asymptomatic carriage rates of Str pneumococcus (2.9 – 5.6%), H Influenzae (1.4%) and viruses (4.3%) were lower than what we found, suggesting that a substantial proportion of our adult subjects represented true infections. (13)(14)

Comparison with existing literature

Only very few studies were published on the relation between microbiological test results in primary care patients and their severity and course of disease. Vos et al who compared course of disease of lower RTI of different viral aetiology and Teepe et al who studied course of disease of bacterial lower RTI saw comparable survival curves as we did in our study.(12)(7) Hopstaken et al also studied signs and symptoms of primary care patients with a lower RTI and could not find clinical predictors who could distinguish viral from bacterial infections, which in in line with our finding that viral and bacterial RTI do not show relevant differences in clinical presentation. (15) Voiriot et al studied patients with severe pneumonia, admitted to an intensive care unit, and found that patients with a mixed viral/bacterial infection did have more severe symptoms and a worse prognosis.(16) In primary care patients with a much milder RTI we could not confirm this finding.

Implications for research and practice

The lack of relevant differences in severity at clinical presentation and course of disease between viral and bacterial infections in primary care patients with flu-like illness questions efforts to distinguish viral from potential bacterial pathogens. Identifying aetiology will only be useful if it has consequences for patient information or treatment. We found that oseltamivir can benefit older patients and those with co-morbidity with influenza like illness. This effect was however not related to identified aetiology.(8) Randomised controlled trials of antibiotic treatment for mild respiratory infections in primary care found no relevant benefit for patients with sinusitis, acute sore throat or acute bronchitis.(17)(18)(19) Studies exploring whether positive bacterial tests in mild respiratory infections modify the effects of antibiotic treatment, found no or only modest effect modification. Seven studies assessed the effects of

antibiotics in patients with acute sore throat and positive throat swabs and saw a somewhat milder and shorter course of disease but irrespective of treatment 90% of patients were better by day 7.(19) In patients with mild lower respiratory tract infections Bruyndonckx et al found that there was a small beneficial effect of amoxicilline treatment in patients in whom a viral and a possible bacterial pathogen were detected but no beneficial effect of antibiotic treatment in all patients with a positive bacterial test.(20) Meanwhile, it is obvious that in extra-ordinary situations like the current COVID pandemic, testing for specific pathogens, like SARS CoV-2, can be highly relevant for patient management and public health purposes. Recently Yu et al showed that budesonide had a beneficial effect in certain subgroups of patients with COVID-19.(21)

In conclusion, pathogen identification by laboratory PCR based testing in primary care patients presenting with ILI, was not associated with meaningful differences in presentation or course of disease. Irrespective of aetiology, illness course was generally self-limiting and lasted for 14 days or less. A wait-and-see policy in most of these patients with ILI seems the best option and given the currently available antimicrobial treatments, and outside pandemics like COVID-19, microbiological testing seems to have limited value.

Funding:
European Commission's Seventh Framework Programme

Ethical approval:
The trial protocol, available online, was approved by National Research Ethics Service Committee South Central—Oxford B. Clinical trial authority approval was obtained from the UK Medicines and Healthcare products Regulatory Agency. All participating countries gained national research ethics committees and clinical trial authority approval as required.

Competing interests:
CCB reports grants from National Institute for Health Research (NIHR) Health as NIHR Senior Investigator, grants from the NIHR Health Technology Assessment Programme to support the study, grants from NIHR Health Protection Research Unit on Health Care Associated Infections and Antimicrobial Resistance, grants from NIHR Health for the MedTech and In Vitro Diagnostics Cooperative for innovative diagnostics and monitoring technology to enhance Community Healthcare during the conduct of the study, personal fees from Pfizer and Roche Molecular Systems, grants from Roche Molecular Diagnostics. AWvdV reports personal fees from Reckitt Benckiser. CLI reports grants from Abbott Diagnostics. HCB or his institute has received, in the 36 months before the submission of this manuscript, grants, support for travelling, consultancy fees, and honoraria from Gilead, BMS, Viiv Healthcare, Idorsia, and Roche, outside the submitted work. He serves as the president of the association contre le HIV et autres infections transmissibles. In this function he has received support from the Swiss HIV Cohort Study from ViiV Healthcare, Gilead, Bristol-Myers Squibb, Merck Sharp & Dohme, and Abbvie. TJV reports grants from the NIHR, Netherlands Organization of Health Research and Development, and the EU Innovative Medicines Initiative, which has Janssen Pharmaceuticals, Biocartis, Janssen, BioMerieux, and Berry Consultants as partners, all outside the submitted work. All other authors declare no competing interests.

Acknowledgements:
We thank all participating general practitioners, other health professionals and patients for their collaboration and commitment in the trial on which data this post hoc analysis was based.

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Tables and figures

Table 1. Baseline characteristics study participants (n=3266)

Age	Child (>1 and ≤12)	479 (14.7%)
	Adult (>12)	2780 (85.3%)
Comorbidity		
	Diabetes	82 (2.5%)
	Chronic respiratory condition	196 (6.0%)
Virus/bacterium*		
	Negative	849 (26.3%)
	Viral	1949 (60.4%)
	Mixed	339 (10.5%)
	Bacterial	90 (2.8%)
Symptoms (major or moderate)		
	Fever	2551 (78.8%)
	Nasal congestion, runny nose	1991 (61.4%)
	Sore throat	1914 (59.5%)
	Headache	2379 (74.6%)
	Cough	2227 (68.7%)
	Muscle aches and / or pains	2286 (72.0%)
	Diarrhoea	170 (5.3%)
	Low energy, tired	2670 (82.6%)
	Not sleeping well	1733 (53.7%)

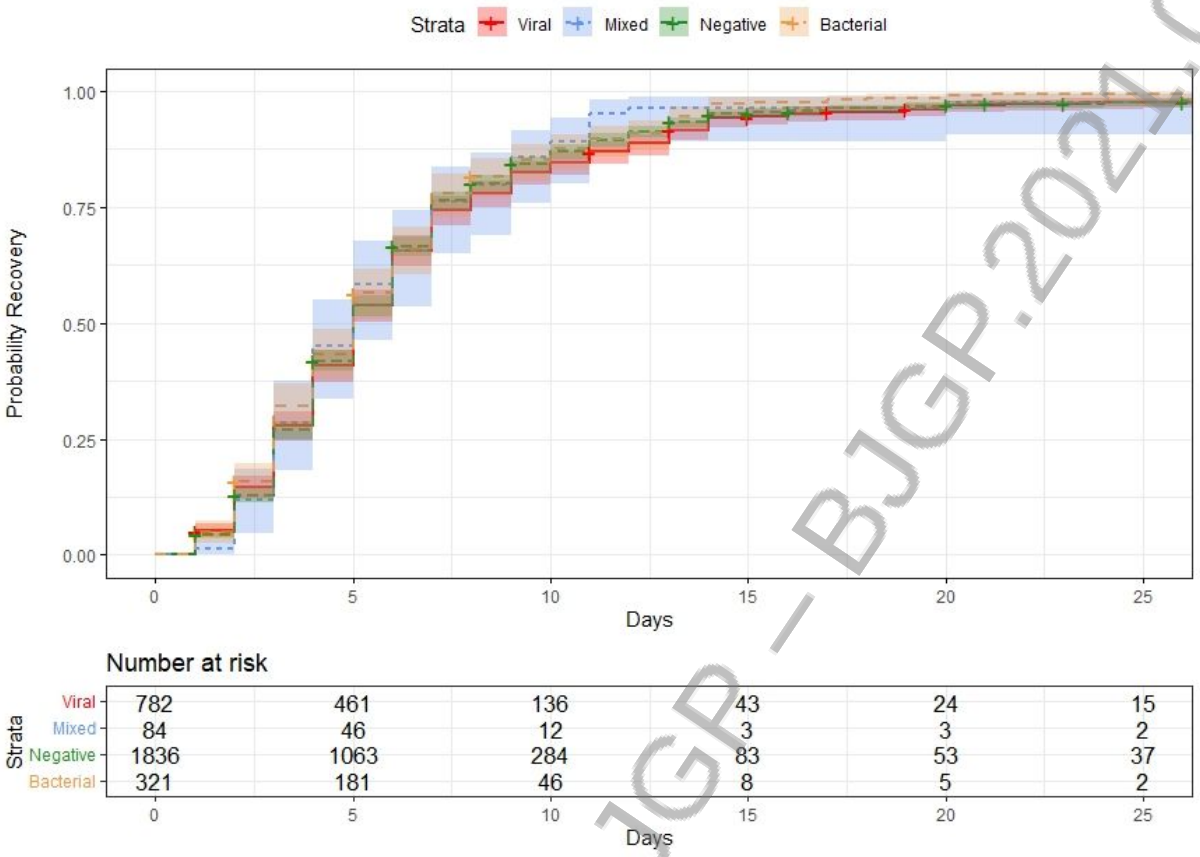
* Negative: presence of no viruses and no bacteria, viral: at least one virus and no bacteria, mixed: and at least one virus and at least one bacterium, bacterial: no viruses and at least one bacterium.

Table 2. Relation between symptom severity at baseline and presence/absence of viruses and/or bacteria, age and previous duration of ILI symptoms

Symptom (outcome)	Effect	OR	95% Wald Confidence Limits	
Fever (N =3199)	Negative vs Viral	0.83	0.68	1.00
	Bacterial vs Viral	0.85	0.50	1.45
	Mixed vs Viral	1.33	0.93	1.91
	Adult vs Child	**0.66**	**0.48**	**0.89**
	Duration ILI symptoms 2 vs 1	0.95	0.77	1.18
	Duration ILI symptoms 3 vs 1	0.85	0.68	1.05
Nasal congestion, runny nose (N= 3204)	**Negative vs Viral**	**0.56**	**0.48**	**0.66**
	Bacterial vs Viral	**0.55**	**0.35**	**0.86**
	Mixed vs Viral	1.02	0.77	1.35
	Adult vs Child	**0.71**	**0.56**	**0.90**
	Duration ILI symptoms 2 vs 1	1.12	0.94	1.34
	Duration ILI symptoms 3 vs 1	1.16	0.96	1.39
Sore throat (N= 3175)	**Negative vs Viral**	**1.29**	**1.09**	**1.52**
	Bacterial vs Viral	1.08	0.69	1.67
	Mixed vs Viral	0.96	0.73	1.26
	Adult vs Child	1.07	0.85	1.36
	Duration ILI symptoms 2 vs 1	0.95	0.80	1.14
	Duration ILI symptoms 3 vs 1	1.05	0.87	1.26
Headache (N=3152)	Negative vs Viral	1.05	0.86	1.27
	Bacterial vs Viral	1.21	0.72	2.02
	Mixed vs Viral	1.01	0.75	1.36
	Adult vs Child	**2.07**	**1.61**	**2.66**
	Duration ILI symptoms 2 vs 1	0.81	0.66	1.00
	Duration ILI symptoms 3 vs 1	0.81	0.66	1.00
Cough (N=3203)	**Negative vs Viral**	**0.39**	**0.33**	**0.46**
	Bacterial vs Viral	**0.42**	**0.27**	**0.65**
	Mixed vs Viral	0.98	0.73	1.32
	Adult vs Child	**1.30**	**1.02**	**1.66**
	Duration ILI symptoms 2 vs 1	**1.31**	**1.09**	**1.58**
	Duration ILI symptoms 3 vs 1	**1.65**	**1.36**	**2.00**
Muscle aches and / or pains (N = 3140)	Negative vs Viral	0.92	0.77	1.11
	Bacterial vs Viral	0.72	0.45	1.16
	Mixed vs Viral	0.84	0.63	1.12
	Adult vs Child	**3.71**	**2.90**	**4.75**
	Duration ILI symptoms 2 vs 1	0.91	0.75	1.12
	Duration ILI symptoms 3 vs 1	0.85	0.69	1.04
Diarrhoea (N = 3189)	Negative vs Viral	**1.50**	**1.06**	**2.12**
	Bacterial vs Viral	0.69	0.21	2.26
	Mixed vs Viral	0.94	0.51	1.74
	Adult vs Child	0.84	0.51	1.38
	Duration ILI symptoms 2 vs 1	1.30	0.85	1.98
	Duration ILI symptoms 3 vs 1	**1.62**	**1.07**	**2.45**
Low energy, tired (N = 3192)	Negative vs Viral	1.02	0.82	1.27
	Bacterial vs Viral	1.38	0.77	2.49
	Mixed vs Viral	1.00	0.72	1.38
	Adult vs Child	**2.31**	**1.77**	**3.01**
	Duration ILI symptoms 2 vs 1	1.18	0.94	1.49
	Duration ILI symptoms 3 vs 1	1.03	0.81	1.30
Not sleeping well (N = 3188)	Negative vs Viral	0.92	0.78	1.09
	Bacterial vs Viral	1.24	0.80	1.93
	Mixed vs Viral	1.14	0.87	1.48
	Adult vs Child	**1.34**	**1.07**	**1.69**
	Duration ILI symptoms 2 vs 1	1.05	0.89	1.26
	Duration ILI symptoms 3 vs 1	1.16	0.97	1.38

Negative: presence of no viruses and no bacteria, bacterial: no viruses and at least one bacterium, viral: at least one virus and no bacteria, mixed: and at least one virus and at least one bacterium. When the confidence interval of the odds ratio includes the 1, the odds of having the symptom in both categories are similar. The confidence intervals that do not include the 1 are highlighted in bold.

Figure 1. Kaplan-Meier curve of time to recovery defined as return to usual activities, with fever, headache, and muscle ache minor or absent for each virus/bacterium class.



The term 'strata' refers to the different levels that can be assumed by the variable that indicates the viral aetiology (with or without a bacterial pathogen), that are: Viral: at least one virus and no bacteria, mixed: at least one virus and at least one bacterium, negative: presence of no viruses and no bacteria, bacterial: no viruses and at least one bacterium.