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Clinical prediction of laboratory-confirmed influenza in adults with influenza-like illness in primary care: a randomized controlled trial secondary analysis in 15 European countries

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Clinical prediction of influenza in adults with influenza-like-illness.

Research Methods.

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KEY MESSAGES

• About 50% of people with influenza symptoms test positive for influenza virus.

• Prediction of influenza is more accurate when based on symptom severity.

• Moderate to major cough, fever, muscle pain and sweat are predictive of flu.
ABSTRACT

Background. Clinical findings do not accurately predict laboratory diagnosis of influenza. Early identification of influenza is considered useful for proper management decisions in primary care.

Objective. We evaluated the diagnostic value of the presence and the severity of symptoms for the diagnosis of laboratory-confirmed influenza infection among adults presenting with influenza-like-illness (ILI) in primary care.

Methods. Secondary analysis of patients with ILI who participated in a clinical trial from 2015 to 2018 in 15 European countries. Patients rated signs and symptoms as absent, minor, moderate or major problem. A nasopharyngeal swab was taken for microbiological identification of influenza and other microorganisms. Models were generated considering 1) the presence of individual symptoms and 2) the severity rating of symptoms.

Results. A total of 2,639 patients aged 18 or older were included in the analysis. The mean age was 41.8 ± 14.7 years, and 1,099 were men (42.1%). Influenza was microbiologically confirmed in 1,337 patients (51.1%). The area under the curve (AUC) of the model for the presence of any of seven symptoms for detecting influenza, was 0.66 (95% CI: 0.65 to 0.68), whereas the AUC of the symptom severity model, which included eight variables – cough, fever, muscle aches, sweating and/or chills, moderate to severe overall disease, age, abdominal pain and sore throat – was 0.70 (95% CI: 0.69 to 0.72).

Conclusion. Clinical prediction of microbiologically-confirmed influenza in adults with ILI is slightly more accurate when based on patient reported symptom severity than when based on the presence or absence of symptoms.

Key words: Clinical Decision Rules; Diagnosis; Human; Influenza, Primary Health Care; Symptom Assessment.
LAY SUMMARY

Influenza is usually diagnosed clinically. However, the accuracy of a diagnosis of influenza based on clinical features is limited because symptoms overlap considerably with those caused by other microorganisms. This study examined whether identification of the severity rather than the presence of key signs and symptoms could aid in the diagnosis of influenza, thereby helping clinicians to determine when antiviral agent use is appropriate. The authors used the database of a previous randomised clinical trial on the effectiveness of an antiviral carried out in primary care centres in 15 countries in Europe during three epidemic periods from 2015/2016 to 2017/2018. Participants with influenza symptoms were included and they were asked about the presence and severity of different symptoms during the baseline visit with their doctors and a nasopharyngeal swab was taken for microbiological analysis. Overall, only 51% of the patients aged 18 or older had a confirmed influenza infection. Clinical findings are not particularly useful for confirming or excluding the diagnosis of influenza. However, the results of our study recommend considering how intense the different symptoms are, since key symptoms rated as moderate or severe are slightly better for predicting flu rather than the presence or absence of these symptoms.
BACKGROUND

Influenza is an important public health issue, with 3–5 million reported cases of severe disease each year, with the highest fatality in those over 65 years of age (> 80% of deaths) [1]. Other viral infections can also be severe, such as the syncytial respiratory virus infection or the recent SARS-CoV-2 infection which has been responsible for millions of deaths [2,3]. Early diagnosis of influenza can be useful for improving the effectiveness of infection prevention and control measures, decreasing the use of antibiotics and increasing appropriate use of antiviral medications, particularly among high-risk populations. In addition, early seasonal diagnosis is often misdiagnosed [4]. Several rapid diagnostic tests have been developed, and although they are easy to use, they all have a poor sensitivity (only 53% sensitivity among adults). That makes them unsuitable for detection of influenza in clinical settings, which is to say that a negative result does not rule out the diagnosis [5]. Molecular diagnosis by reverse transcriptase polymerase chain reaction (PCR) is more sensitive, but they are still more expensive than other tests [2]. Isolation of the virus by conventional culture takes about a week and is not practical for diagnosis.

Diagnosis in primary care is usually mainly based on clinical and epidemiological criteria (high fever, myalgia, headache, general malaise and non-productive cough). None of these criteria are specific, and these symptoms can be caused by numerous respiratory viruses [6]. In primary care, only half of the possible cases during flu seasons are actually influenza, as other viruses can mimic influenza infection and, also, some individuals who are sick with influenza virus infection do not have high temperature, especially those who are elderly or immunosuppressed [7]. Many studies have evaluated the validity of different symptoms or case definitions of the influenza syndrome. However, the application and interpretation of the findings of these studies are hampered by different methodologies, different clinical settings, different inclusion criteria, and inconsistent conclusions [8]. In epidemic periods, the presence of fever and cough in the first 48 hours are the symptoms that best indicate the presence of influenza infection, reaching a positive predictive value of more than 80%; in contrast, odynophagia is negatively associated [9].
The ALIC⁴E study was a multicentre European clinical trial in different European networks which evaluated the effectiveness of oseltamivir in patients with influenza-like-illness (ILI) [10]. Patients were asked about the severity of different symptoms during the baseline visit with their GPs. The objective of this secondary analysis was to assess (i) whether symptom severity is more strongly associated with the presence of laboratory confirmed influenza infection during seasonal influenza epidemics than symptom presence alone, and (ii) whether inclusion of symptom severity might improve the performance of a clinical diagnostic prediction model.

METHODS

Design

Post-hoc analysis of the sample of patients over 18 years of age with ILI of ≤72 hours from symptom onset recruited in a randomised clinical trial on the effectiveness of oseltamivir carried out in primary care centres in 20 clinical research networks in 15 European countries over three consecutive influenza seasons from 2015/2016 to 2017/2018. The protocol of this trial has been published previously [11]. The STARD checklist was used (Appendix).

Study population

In brief, GPs were asked to recruit patients with ILI, defined as the self-reported presence of sudden onset fever combined with at least one respiratory symptom (cough, sore throat, runny or blocked nose) and at least one systemic symptom (headache, muscle pain, sweating, chills or tiredness) [11,12]. Each season’s recruitment period was based on reports of national incidences of ILI presentation rising above or falling below country-specific thresholds, using information from the European Centre of Disease Prevention and Control and regional sources for each network [13]. At the baseline visit GPs collected information about age, sex, relevant comorbidities, duration of symptoms and the clinician’s rating of overall ILI severity as mild, moderate or severe. This variable was then dichotomized in mild and moderate-to-severe. In addition, during the visit the patients, independent of the GP assessment, were asked to complete a self-report checklist of symptoms
including rating of the severity of the sensation of fever felt at that time, as well as the severity of nasal congestion, sore throat, headache, cough, shortness of breath, muscle pain, sweats/chills, diarrhoea, nausea/vomits, abdominal pain, low energy or tiredness, difficulties sleeping, dizziness and a feeling of general malaise, and these were scored on a Likert scale as not present, minor problem, moderate problem or major problem. Symptom severity was dichotomised in major and moderate vs. minor and no problem.

During this baseline visit, a nasopharyngeal swab (COPAN®) was taken from each patient, stored in frozen universal transport medium a maximum of 24 hours after extraction. This was then centrally analysed at the Laboratory of Medical Microbiology of the University of Antwerp (Belgium) using a Multiplex Real Time PCR for the detection of pathogenic genes from Fast Track Diagnostics 21 (Fast Track Diagnostics, Luxembourg), which analyses the presence of influenza virus A and B, and other respiratory viruses and bacteria [14].

**Statistical methods**
The absolute frequencies of the microbiological analyses were determined. Sociodemographic, clinical characteristics, and presence (yes/no) and severity (moderate to major vs. absent or minor) of symptoms, were compared with those with and without microbiological confirmation of influenza virus infection using the Chi-square and Student’s t tests. Univariable associations of symptoms and symptom severity with laboratory-confirmed infection were also estimated by odds ratios with 95% confidence intervals (CI) using logistic regression. For the multivariable analysis, we fitted generalised linear mixed models (GLMM) discarding associations that were non-significant, and the final set of predictors were obtained by means of Akaike Information Criterion-based stepwise backward algorithm [15]. Incomplete observations (113 of the 2,639 individuals) were removed, numerical variables were scaled and centred, parameters were optimized using the BOBYQA algorithm [16], and GLMM accounted for site as random effect on the intercept. To assess the performance of each model, we used the area under the receiver operating characteristic curve (AUC) with 95% CI. In a sensitivity analysis, we fitted two models with four symptoms that can be
easily recorded during daily clinical practice: fever, cough, muscle aches and sweats and/or chills and compared their performance against the complete model. Statistically significant differences were considered with p <0.05. All analyses were performed using R v3.6.3 and SPSS v24.

RESULTS

A total of 2,639 patients aged 18 years or older with ILI were included in the analysis. The mean age was 41.8 ± 14.7 years, and 1,099 were male (42.1%). A total of 1,337 patients were tested positive for influenza virus (51.1%). Table 1 describes the sociodemographic and clinical characteristics of the subjects with true influenza infection and those with other aetiology. Patients with influenza were older and their overall illness severity was rated as more severe by their clinicians than patients with other aetiology. As shown in table 2, cough and feeling feverish were more frequent in the group of patients with influenza compared to those without, with an OR of 3.74 (95% CI: 2.74 to 5.11) and 1.99 (95% CI, 1.41 to 2.81), respectively. Similarly, these symptoms were rated as more severe among patients with microbiologically confirmed influenza (OR 2.99, 95% CI: 2.51 to 3.56 and 1.91, 95% CI: 1.59 to 2.31, respectively).

Regarding the presence of signs and symptoms, patients with influenza infection were more likely to have cough (odds ratio [OR] 3.61; 95% CI: 2.60 to 5.02), fever (OR 1.99, 95% CI: 1.36 to 2.92), clinician’s rating of overall illness severity as moderate to severe (OR 1.81, 95% CI: 1.44 to 2.26), dizziness (OR 1.26, 95% CI: 1.06 to 1.49) and were older (OR 1.18, 95% CI: 1.09 to 1.29) in the GLMM. Conversely, the presence of diarrhoea and sore throat were associated with a reduced odds of influenza (OR 0.72, 95% CI: 0.56 to 0.92 and OR 0.74, 95% CI: 0.58 to 0.94, respectively) (Fig. 1A). In relation to the severity of symptoms, influenza infection was associated with moderate-to-major cough (OR 3.13; 95% CI: 2.57 to 3.80), moderate-to-major feeling feverish (OR 1.69, 95 CI%: 1.36 to 2.11), moderate to severe overall illness severity rating (OR 1.55, 95% CI: 1.23 to 1.96), moderate-to-major muscle aches (OR 1.39, 95% CI: 1.12 to 1.73), moderate-to-major sweats and/or chills (OR 1.24, 95% CI: 1.01 to 1.53), age (OR 1.14: 95% 1.04 to 1.24), and inversely to moderate-to-major
abdominal pain (OR 0.68, 95% CI: 0.49 to 0.95) and moderate-to-major sore throat (OR 0.63, 95% CI: 0.52 to 0.75) (Fig. 1B).

As shown in figure 2, the AUC of the symptoms present/absent model for detecting influenza, which included the seven variables mentioned before, was 0.66 (95% CI: 0.65 to 0.68). The AUC of the symptom severity model included eight variables and performed better in predicting influenza infection (0.70; 95% CI: 0.69 to 0.72) whereas the short version of this severity model including only fever, cough, muscle aches and sweats and/or chills presented an AUC of 0.67 (95% CI: 0.63 to 0.72).

**DISCUSSION**

Approximately half of the patients with ILI during a seasonal influenza epidemic were found to have microbiologically-confirmed influenza infection. Unlike other studies, we included an evaluation of the severity of symptoms in our prediction models. Clinical findings are not particularly useful for confirming or excluding the diagnosis of influenza in adults with ILI. However, we found that a prediction rule based on moderate or major cough, fever, muscle aches, sweats/chills and the judgement of moderate or severe ILI by the clinician, increasing age, and absence or mild sore throat and abdominal pain are slightly better for diagnosing influenza infection than only the use of the presence or absence of particular symptoms, as the prediction improved to 70%. Even considering only the first four criteria the prediction of influenza can be improved to 67%.

**Strengths and limitations of the study**

The major strength of this study is the large number of patients included, with more than 2,600 adults with ILI symptoms, and the extensive baseline information collected. All patients included in this study participated in a clinical trial on the effectiveness of oseltamivir. Therefore, all patients provided informed consent to participate in the study. We do not know how many patients refused to participate as not all participating investigators recorded this information. Therefore, we do not know if the patients who declined to participate were different from those who were included. One of the exclusion criteria of this study was the previous duration of symptoms, since only those with
three or fewer days of symptoms were eligible. However, all the participants met the inclusion criteria for ILI. Although many researchers participated in the study and the rate of symptoms might be different across professionals and settings, all patients had to meet a series of criteria for inclusion. Thus, all individuals had homogeneous ILI symptoms, thereby reproducing usual practice in primary care where all these patients would have been diagnosed with syndromic ILI instead of labelling with aetiology. Participants presented to the clinician primarily with a mild syndrome (ILI) and therefore, the results of this study are only generalisable to patients who are seen with ILI symptoms in primary care. Nearly 10% of the patients included were vaccinated against influenza and the severity of the infection might have been lighter as a result.

**Comparison with existing literature**

Viral respiratory tract infections are a major public health problem due to their ease of transmission, wide occurrence and substantial morbidity. Although viral respiratory tract infections in patients presenting to primary care are usually self-limiting, infections in individuals with chronic diseases and in old people are typically more severe, with prolonged symptoms and an increased risk of complications. Identifying some specific viruses might therefore be particularly useful. The current COVID-19 pandemic has showed that new viral strains can have a specific morbidity and mortality and testing for SARS-CoV-2 has become relevant. Similarly, identifying influenza virus infection might be important as new antivirals drugs are being developed against influenza viruses [17]. Point-of-care testing using rapid influenza diagnostic tests, which are often used for diagnosis by physician offices and emergency centres, lack sensitivity. Testing by PCR is, however, highly sensitive and specific, but these point-of-care tests are still expensive. Thus, clinicians frequently rely on a clinical diagnosis of influenza to inform early decision-making.

Self-diagnostic related information has recently shown to be associated with influenza, especially when patients self-report an extremely high probability [18]. However, this information was not collected in our study, but clinician judgement of the overall influenza severity was included in the two models, as the diagnosis was more likely when the doctors considered the infection to be more
severe. In the present study, patients were asked about the severity of the symptoms they had, trying to reproduce what is done in daily primary care clinical practice when patients explain how they experience their symptoms. We chose to dichotomise the symptoms as mild versus moderate and major because this is understandable for patients and physicians and clinicians focus on symptoms that are moderate or severe. Using symptoms rated as moderate and major is increasingly being used by more researchers in studies on respiratory tract infections, but so far, they have not been used for influenza infection. Therefore, we cannot directly compare our results with other studies. The prevalence of influenza infection found in our study is comparable with other studies. Michiels et al found a prevalence of influenza of 52% [19] and of 42% in another study conducted in an emergency department [20]. Various systematic reviews on the role of signs and symptoms in the diagnosis of influenza show that they are not particularly helpful for confirming or discarding infection [19,21-23]. Some studies have observed that viruses other than influenza virus can cause a comparable burden of disease as influenza viruses [22,24]. In our sample, the best predictors for laboratory-confirmed influenza were cough followed by fever, with ORs of 3.61 and 1.99, respectively. These findings are consistent with those of several other studies, where cough and fever ranked first and second as well [19,25-27]. Also, in the GRACE study, patients with fever, cough, and chills had a higher percentage of influenza [27].

The AUC results obtained in our study are suboptimal for correct diagnosis of influenza. Considering the complete version of moderate to major symptoms in patients presenting with a sudden onset fever combined with at least one respiratory and one systemic symptom during seasonal influenza infection, there is a probability of 0.7 of correctly identifying a person as having or not having influenza, being slightly better than using the presence of symptoms alone. However, when considering the severity of only four symptoms—feeling feverish, cough, muscle aches and sweats and/or chills—, the probability of diagnosing of influenza is slightly better than considering the seven symptoms of the presence/absence model (0.67 vs. 0.66). From a clinical standpoint we therefore
suggest considering the intensity of these four symptoms for better predicting the diagnosis of influenza infection.

Conclusions
In summary, clinical findings are not particularly useful for confirming or excluding the diagnosis of influenza in adults presenting to primary care with ILI. Based on our results we recommend considering moderate or major ILI symptoms rather than simply considering the presence of symptoms for predicting influenza infection. This can easily be implemented in the primary care clinical setting to rapidly identify and treat those potential influenza cases, as well as assist public health institutes with monitoring and surveillance of influenza outbreaks.

DECLARATION

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Conflict of interest: 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. 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. 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. CL reports grants from Abbott Diagnostics. All other authors declare no competing interests.

Data Availability Statement: The data underlying this article will be shared on reasonable request to the corresponding author.

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FIGURE LEGENDS

Figure 1. Multivariable analysis of symptoms associated with laboratory-confirmed influenza. A: presence of symptoms. B: presence of moderate-to-major symptoms.

Figure 2. ROC curves of the two models of symptoms (presence and severity of symptoms), including the complete and short versions, for predicting laboratory-confirmed influenza infection.
Table 1. Baseline characteristics of the patients included in the study. Data collected from January 2016 to April, 2018

<table>
<thead>
<tr>
<th></th>
<th>Patients without influenza (n=1277)</th>
<th>Patients with confirmed influenza (n=1337)</th>
<th>All patients (n=2614)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr (SD)</td>
<td>40.3 (14.8)</td>
<td>43.2 (14.5)</td>
<td>41.8 (14.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Male, n (%)</td>
<td>520 (40.7)</td>
<td>579 (43.3)</td>
<td>1099 (42.1)</td>
<td>0.094</td>
</tr>
<tr>
<td>- Female, n (%)</td>
<td>757 (59.3)</td>
<td>757 (56.7)</td>
<td>1514 (57.9)</td>
<td></td>
</tr>
<tr>
<td>Influenza vaccination in the last 6 months, n (%)</td>
<td>148 (11.6)</td>
<td>118 (8.8)</td>
<td>266 (10.2)</td>
<td>0.065</td>
</tr>
<tr>
<td>Relevant comorbidity**, n (%)</td>
<td>209 (16.4)</td>
<td>211 (15.8)</td>
<td>420 (16.1)</td>
<td>0.362</td>
</tr>
<tr>
<td>Prior duration of symptoms</td>
<td></td>
<td></td>
<td></td>
<td>0.052</td>
</tr>
<tr>
<td>- Less than 24 hours, n (%)</td>
<td>382 (29.9)</td>
<td>343 (25.7)</td>
<td>725 (27.7)</td>
<td></td>
</tr>
<tr>
<td>- Between one and two days, n (%)</td>
<td>480 (37.6)</td>
<td>536 (40.1)</td>
<td>1016 (38.9)</td>
<td></td>
</tr>
<tr>
<td>- Between two and three days, n (%)</td>
<td>415 (32.5)</td>
<td>458 (34.3)</td>
<td>873 (33.4)</td>
<td></td>
</tr>
<tr>
<td>Clinician overall ILI severity rating, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>- Mild</td>
<td>308 (24.1)</td>
<td>194 (14.5)</td>
<td>502 (19.2)</td>
<td></td>
</tr>
<tr>
<td>- Moderate</td>
<td>780 (61.1)</td>
<td>820 (61.3)</td>
<td>1600 (61.2)</td>
<td></td>
</tr>
<tr>
<td>- Severe</td>
<td>189 (14.8)</td>
<td>323 (24.2)</td>
<td>512 (19.6)</td>
<td></td>
</tr>
</tbody>
</table>

*Two-sided p-value from chi-square or t-test for categorical and numerical variables.

**Any of the following conditions: cardiovascular disease, diabetes, chronic respiratory condition, hepatic, haematologic, neurologic or neurodevelopmental condition, transient ischaemic accident, overnight hospital admission in the last year.
<p>| Table 2. Symptoms of the patients in the baseline visit. Data collected from January 2016 to April, 2018 |
|---|---|---|---|---|---|---|---|---|---|
| | Yes/No | Presence of symptoms (yes vs. no) | Severity of symptoms (moderate or major vs. minor or absent) |
| | Patients without influenza | Patients with confirmed influenza | OR (95% CI) | P-value | Patients without influenza | Patients with confirmed influenza | OR (95% CI) | P-value |
| Feeling feverish | Yes | 1176 (92.5) | 1280 (96.1) | 1.99 (1.41 to 2.81) | &lt;0.001 | 911 (71.7) | 1104 (82.9) | 1.91 (1.59 to 2.31) | &lt;0.001 |
| | No | 95 (7.5) | 52 (3.9) | 360 (28.3) | 228 (17.1) |
| Nasal congestion or runny nose | Yes | 1071 (84.2) | 1157 (86.7) | 1.23 (0.99 to 1.53) | 0.067 | 750 (59.0) | 809 (60.6) | 1.07 (0.92 to 1.25) | 0.381 |
| | No | 201 (15.8) | 177 (13.3) | 522 (41.0) | 525 (39.4) |
| Sore throat | Yes | 1101 (86.4) | 1105 (82.9) | 0.77 (0.62 to 0.95) | 0.015 | 813 (63.8) | 732 (54.9) | 0.69 (0.59 to 0.81) | &lt;0.001 |
| | No | 174 (13.6) | 228 (17.1) | 462 (36.2) | 601 (45.1) |
| Headache | Yes | 1182 (92.8) | 1239 (92.8) | 1.00 (0.75 to 1.35) | 0.976 | 968 (76.0) | 1028 (77.0) | 1.06 (0.88 to 1.27) | 0.538 |
| | No | 92 (7.2) | 96 (7.2) | 306 (24.0) | 307 (23.0) |
| Cough | Yes | 1096 (85.9) | 1276 (95.8) | 3.74 (2.74 to 5.11) | &lt;0.001 | 734 (57.5) | 1068 (80.2) | 2.99 (2.51 to 3.56) | &lt;0.001 |
| | No | 180 (14.1) | 56 (4.2) | 542 (42.5) | 264 (19.8) |</p>
<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes</th>
<th>No</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
<th>Yes</th>
<th>No</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortness of breath</td>
<td>637 (50.2)</td>
<td>631 (49.8)</td>
<td>1.11 (0.95 to 1.29)</td>
<td>0.202</td>
<td>306 (24.1)</td>
<td>962 (75.9)</td>
<td>1.11 (0.93 to 1.32)</td>
<td>0.264</td>
</tr>
<tr>
<td>Muscle aches and/or pain</td>
<td>1188 (93.5)</td>
<td>83 (6.5)</td>
<td>1.08 (0.79 to 1.48)</td>
<td>0.637</td>
<td>929 (73.1)</td>
<td>342 (26.9)</td>
<td>1.63 (1.36 to 1.97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sweats and/or chills</td>
<td>1120 (88.1)</td>
<td>151 (11.9)</td>
<td>1.37 (1.07 to 1.77)</td>
<td>0.014</td>
<td>851 (67.0)</td>
<td>420 (33.0)</td>
<td>1.60 (1.35 to 1.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>188 (14.8)</td>
<td>1079 (85.2)</td>
<td>0.74 (0.59 to 0.93)</td>
<td>0.010</td>
<td>75 (5.9)</td>
<td>1192 (94.1)</td>
<td>0.74 (0.52 to 1.05)</td>
<td>0.089</td>
</tr>
<tr>
<td>Nausea and/or vomiting</td>
<td>330 (26.0)</td>
<td>939 (74.0)</td>
<td>0.99 (0.83 to 1.18)</td>
<td>0.926</td>
<td>127 (10.0)</td>
<td>1142 (90.0)</td>
<td>0.82 (0.63 to 1.07)</td>
<td>0.141</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>267 (21.1)</td>
<td>999 (78.9)</td>
<td>0.97 (0.8 to 1.17)</td>
<td>0.731</td>
<td>114 (9.0)</td>
<td>1152 (91.0)</td>
<td>0.71 (0.53 to 0.95)</td>
<td>0.020</td>
</tr>
<tr>
<td>Low energy and/or tiredness</td>
<td>1227 (96.6)</td>
<td>43 (3.4)</td>
<td>1.57 (0.97 to 2.53)</td>
<td>0.064</td>
<td>1064 (83.8)</td>
<td>206 (16.2)</td>
<td>1.19 (0.96 to 1.48)</td>
<td>0.113</td>
</tr>
<tr>
<td>Not sleeping well</td>
<td>934 (73.8)</td>
<td>332 (26.2)</td>
<td>1.31 (1.09 to 1.57)</td>
<td>0.004</td>
<td>664 (52.4)</td>
<td>602 (47.6)</td>
<td>1.16 (0.99 to 1.35)</td>
<td>0.065</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Odds Ratio (CI)</td>
<td>P-value</td>
<td>Yes</td>
<td>No</td>
<td>Odds Ratio (CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------</td>
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<td>---------</td>
<td>-----------</td>
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<td>----------------</td>
<td>---------</td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>578 (45.4)</td>
<td>694 (54.6)</td>
<td>1.28 (1.09 to 1.49)</td>
<td>0.002</td>
<td>290 (22.8)</td>
<td>982 (77.2)</td>
<td>1.28 (1.07 to 1.53)</td>
<td>0.007</td>
</tr>
<tr>
<td>Feeling generally unwell</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1234 (97.4)</td>
<td>33 (2.6)</td>
<td>1.39 (0.82 to 2.35)</td>
<td>0.213</td>
<td>1116 (88.1)</td>
<td>151 (11.9)</td>
<td>1.59 (1.22 to 2.07)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

OR=Odds ratio; CI=Confidence interval