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Retrospective study of the use of an influenza disease two-tiered classification system to characterize clinical severity in US children

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ABSTRACT

In children <5 years, influenza is associated with higher risk of serious disease and hospitalization when compared with other age groups. Influenza vaccination reduces the risk of influenza and vaccination may attenuate the severity of disease. Recent studies in Europe suggest that classifying influenza disease as mild versus moderate-to-severe (M-S) using a novel definition may be clinically significant. We retrospectively evaluated whether this M-S definition also characterized influenza severity in a cohort of US children. We included children <18 years at Kaiser Permanente Northern California with PCR-confirmed influenza during the 2013–2014 influenza season. We classified children as M-S if they had ≥1 symptom: fever >39°C, acute otitis media, lower respiratory tract infection (LRTI), or extra-pulmonary complications; otherwise, they were classified as mild. We used multivariable log-binomial models to assess whether M-S influenza disease was associated with increased healthcare utilization. Nearly half of the 1,105 influenza positive children were classified as M-S. Children 6–35 months had the highest proportion of M-S disease (35.1%), mostly due to LRTI (63.2%) and fever (44.6%). Children ≥6 months who had M-S disease were associated with a 1.6 to 2.8 times increased likelihood of having had an emergency department or any follow-up outpatient visits. Those who had M-S disease were associated with an increased likelihood of receiving antibiotics, with the highest likelihood in children 6–35 months (RR 9.0, 95% CI 4.1, 19.8). While more studies are needed, an influenza classification system may distinguish children with more clinically significant disease.

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Introduction

Infection with influenza viruses can result in mild to severe respiratory illness, and rarely death. In children aged <5 years, and particularly among those aged <2 years, influenza is associated with higher risk of serious complications and hospitalization, with rates similar to those seen in elderly populations.[1] The Centers for Disease Control and Prevention recommend annual influenza vaccination for everyone starting at 6 months of age.

Influenza vaccination reduces the risk of influenza and may attenuate the severity of influenza illness.[2] Clinical severity classification systems have been developed for other vaccine-preventable diseases, such as rotavirus gastroenteritis and varicella, and studies have found that vaccination provides greater vaccine effectiveness against severe disease.[3,4] Distinguishing mild influenza from clinically significant disease could similarly be useful when assessing how well current and new influenza vaccines protect against a range of influenza severity. An influenza classification system could more precisely evaluate how well influenza vaccination attenuates differing disease severity and improve our understanding of the morbidity associated with severe influenza. There is no generally accepted definition for moderate-to-severe (M-S) influenza versus mild disease to date.

Several recent studies conducted outside of the United States (US) have suggested that an M-S influenza disease classification may distinguish influenza disease representing the upper tercile of clinical severity. In a phase 3 efficacy study of an inactivated quadrivalent influenza vaccine (QIV) in children aged 3 to 8 years, QIV had higher vaccine efficacy against laboratory-confirmed M-S influenza (73%) than against any severity (55%).[5] Another phase 3 multinational trial similarly found QIV efficacy to be higher against M-S disease (63%) versus any severity (50%) in children aged 6–35 months.[6] A prospective cohort study in Finland found that children aged <13 years with M-S influenza had significantly longer durations of fever, were more likely to receive any antibiotic treatment, and in *post hoc* analysis, were the only cases with any emergency department (ED) visits or hospitalizations.[7] Another prospective cohort study in Germany reported that M-S influenza was associated with more healthcare utilization among children aged 1 to 5 years.[8]

Whether the M-S definition utilized in the above studies characterizes influenza disease severity in US children is not known. We therefore sought to use this influenza severity definition, which differs from the currently accepted World Health Organization (WHO) severe acute respiratory infections (SARI) definition.[5] We retrospectively classified children with confirmed influenza within

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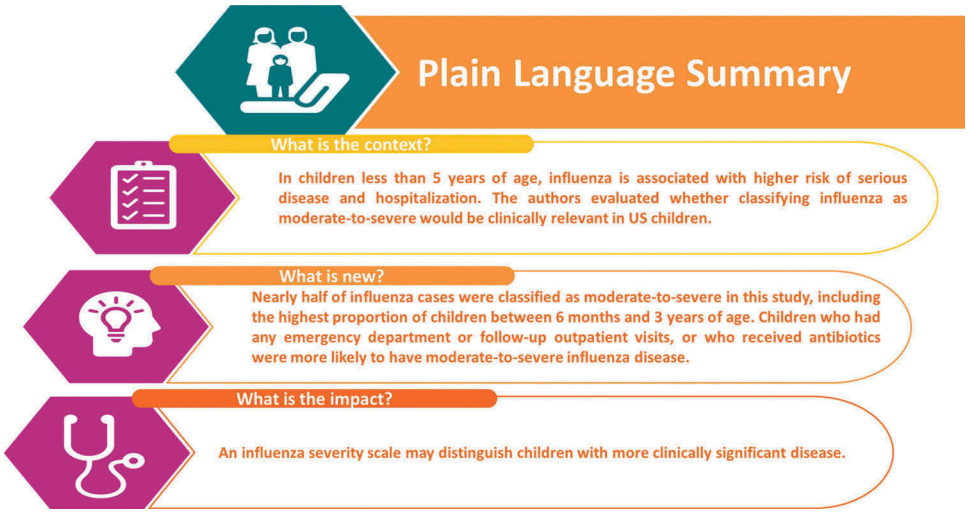

Figure 1. Plain language summary

Kaiser Permanente Northern California (KPNC) as having M-S or mild influenza disease and assessed whether having M-S disease was associated with an increased likelihood of utilizing healthcare.

Materials and methods

Setting

We conducted a retrospective cohort study using data from KPNC, an integrated healthcare delivery system with an annual membership of approximately 4million, 20% of whom are aged <18 years. Members receive nearly all their care at KPNC-owned facilities, including 65 medical clinics and 27 hospitals. All inpatient, outpatient, and ED diagnoses, laboratory tests, immunizations, therapeutic services, radiology tests, and medications are captured in KPNC's electronic medical record.

KPNC has used reverse transcription polymerase chain reaction (PCR) to test for influenza since 2006 during the influenza seasons, which generally runs from October through April of the following year (but may be earlier or later depending on circulating influenza virus). KPNC routinely used the Cepheid GeneXpert PCR assay, which required a nasopharyngeal or nasal swab specimen for the detection of influenza A, influenza B, and/or respiratory syncytial virus (RSV). No additional testing was performed to detect influenza subtypes. Most pediatric influenza cases were diagnosed in KPNC's outpatient clinics and testing was at the discretion of the treating pediatrician. PCR testing often continues throughout the winter respiratory season to identify either influenza or RSV viruses.

The KPNC Institutional Review Board approved this study.

Study population

We included all KPNC members who were aged <18 years at the time of the PCR test, and who had a positive test for influenza A or B during the 2013–2014 influenza season (from September 1, 2013, to April 30, 2014). We included individuals who were KPNC members on the day of their PCR test through at least the subsequent 14 days to capture all outcomes of interest. Since all KPNC members have health insurance, the study population only included insured individuals.

Classifying influenza disease

We categorized all cases as having either M-S or mild influenza disease based on the occurrence of one or more of the following during the 7 days before and after the PCR test date using four broad M-S criteria categories:[51] documented body temperature >39°C (>102.2°F);[2] physician-confirmed acute otitis media (AOM);[3] physician-confirmed lower respiratory tract illness (LRTI); or[4] physician-diagnosed serious extra-pulmonary complications (e.g., myositis, encephalitis, seizures, or myocarditis). Patients with none of these criteria were classified as having "mild" influenza.

To assess for fever, we used temperatures >39°C as recorded in the electronic medical record during the encounter. To identify AOM, LRTI, and extra-pulmonary complications, we compiled an initial list of the most relevant codes from the International Classification of Diseases, Ninth Revision (ICD-9) and KPNC internal diagnostic codes. Using an iterative process which involved all study authors, we further validated, refined, and reviewed the diagnosis codes that appeared in our cohort to create the final list of M-S classification codes (Appendix A1).

Outcomes

We evaluated for the occurrence of several outcomes during the 14 days after the positive influenza test. The primary outcomes included hospitalization, admission to the intensive care unit (ICU), and receipt of systemic antibiotics and/or antivirals (i.e., neuraminidase inhibitors) (Appendix A2); secondary outcomes included follow-up outpatient visits, ED visits, bacterial/fungal co-infection (based on positive blood culture), C-reactive protein value, and inpatient supplemental oxygen use. While antibiotic use as an outcome may be related to components of

the M-S influenza disease definition (i.e., diagnosis of AOM and/or LRTI), we included this outcome for comparative purposes because it was also assessed in prior evaluations of this M-S definition.[7,8]

Covariates

We used ICD-9 codes to identify comorbid conditions (Appendix A3). We included conditions diagnosed at least 90 days prior to the PCR test to ensure that the condition was chronic rather than acutely related to influenza disease. We categorized influenza vaccination as "current season" if it was received at least 14 days prior to the influenza PCR test date to allow for antibodies to develop. We considered an individual as influenza primed if they received at least one dose of influenza vaccine during the prior 2012–2013 influenza season, or if they received at least two doses of influenza vaccine since July 2010. We considered a PCR test date as "early" in the influenza season if it occurred prior to January 12, 2014 (the median collection date for the cohort), and "late" if it was on or after this date.

Statistical analysis

The aim was to characterize whether PCR-positive cases were associated with an increased likelihood of healthcare utilization outcomes of interest for those with M-S versus mild disease. There were insufficient number of cases (n < 5) for several outcomes and we were only able to perform multivariable analyses for receipt of antivirals, receipt of antibiotics, any follow-up outpatient visit, and any ED visit.

We conducted separate multivariable log-binomial model analyses using SAS 9.2 (SAS Institute, Cary NC), assuming a binomial distribution and using the log link function to assess each healthcare utilization outcome. Log-binomial regression models are appropriate to estimate relative risk (RR) for cross-sectional studies with common outcomes.[9] We adjusted all models for sex, vaccination in the current season (yes/no), vaccinated in prior season (yes/no), PCR test time (early/late), and comorbid conditions (yes/no). We used the following four age groups: <6 months, ≥6 to <36 months, ≥3 to <9 years, and ≥9 to <18 years. In particular, the ≥6 to <36 months and ≥3 to <9 years age groupings were included to be consistent with previous phase 3 efficacy studies that used the same novel M-S influenza disease classification.[5,6] We did not include race/ethnicity, influenza type, and presence of RSV co-infection in our models due to insufficient variation when stratified by outcome. Pearson's Chi-squared test (or Fisher's Exact Test) was used to determine whether there was a significant difference between mild versus M-S cases for each of the outcomes.

Results

In the 2013–2014 influenza season, there were 8,321 PCR tests performed among all children aged <18 years, of which 1,146 (13.8%) were positive. Forty-one cases were not members during the follow-up period for outcomes and were thus excluded. Our final cohort consisted of 1,105 children, most of whom were diagnosed with Influenza A (85.8%; Table 1). Two hundred and thirty-six children (21.4%) received an influenza vaccine, 57 (5.2%) were unvaccinated due to age <6 months, and 349 (31.6%) were "primed" with a prior dose of an influenza vaccine. We classified 538 (48.7%) as M-S influenza and 567 (51.3%) as mild.

The most frequent M-S symptom was LRTI (63.2%), followed by fever >39°C (44.6%; Table 2). Among children with a single M-S symptom, "LRTI only" was the most common (n = 218, 40.5%), followed by "fever >39°C only" (n = 135; 25.1%). Among children with >1 symptom, the most common combination was LRTI together with fever >39°C (n = 72; 13.4%).

In bivariable analyses, children with M-S influenza had significantly more hospitalizations, receipt of antibiotics, ED visits, and follow-up outpatient visits than did children with mild disease ($p < .01$), although there was no difference in antiviral use (Table 3). Most of those hospitalized (38/40) and all those admitted to the intensive care unit (6/6) had M-S influenza (Table 3).

In multivariable analyses, children with M-S disease aged ≥6 months were associated with a 2.5–2.8 times increased likelihood of seeking care in an ED setting (Table 4). Children with M-S disease aged ≥6 months were also associated with a 1.6–2.3 times increased likelihood of follow-up outpatient visits, with children ≥3 to <9 years having the greatest increased likelihood of having a follow-up outpatient visit (RR 2.3, 95% CI 1.7, 3.3). Children with M-S disease aged ≥6 months were also associated with a significantly increased likelihood of receiving antibiotics, and those aged ≥6 to <36 months had the highest increased likelihood of receiving antibiotics (RR 9.0, 95% CI 4.1, 19.8). Those who received antibiotics had an increased likelihood of having comorbidities (RR 1.5, 95% CI: 1.1, 1.9) or having received influenza vaccine in the current season (RR 1.3, 95% CI 1.01, 1.7).

Children with M-S influenza were not associated with an increased likelihood of receiving antiviral medication. However, among those who did receive antiviral medication, children aged ≥3 to <9 years were at increased likelihood of having comorbidities (RR 1.3, 95% CI 1.03, 1.7), while children aged ≥9 to <18 years were at increased likelihood of having been diagnosed with influenza later in the influenza season (RR 1.4, 95% CI 1.1, 1.7).

Discussion

In this study, we used a novel influenza severity definition that has been utilized in other (non-US) clinical and observational studies[5-8] to characterize whether US children classified retrospectively as having moderate-to-severe influenza disease had an increased likelihood of utilizing healthcare, including having antibiotics or antivirals prescribed. Overall, this study found that children identified as having moderate-to-severe disease had an increased likelihood of being prescribed antibiotics, having ED visits, and subsequent outpatient visits when compared with children with mild disease. Interestingly, however, severity was not associated with an increased likelihood of receiving antiviral medication.

When compared to the WHO SARI definition, this two-tiered classification system may have greater utility in healthcare settings such as KPNC, which tests thousands of individuals each year for influenza. The WHO defines a SARI case based

Table 1. Characteristics of children with mild and moderate-to-severe influenza at Kaiser Permanente Northern California, 2013–2014 influenza season.

Characteristic	Mild, n = 567 (%)	Moderate-to-severe, n = 538 (%)
Sex		
Male	293 (51.7)	293 (54.5)
Female	274 (48.3)	245 (45.5)
Age		
<6 months	24 (4.2)	33 (6.1)
≥6 to <36 months	104 (18.3)	189 (35.1)
≥3 to <9 years	212 (37.4)	177 (32.9)
≥9 to <18 years	227 (40.0)	139 (25.8)
Race		
Asian	100 (17.6)	95 (17.7)
Black	44 (7.8)	45 (8.4)
Hispanic	184 (32.5)	185 (34.4)
Multiracial	33 (5.8)	41 (7.6)
Native American	2 (0.4)	1 (0.2)
Pacific Islander	4 (0.7)	2 (0.4)
Unknown/Other	7 (1.2)	4 (0.7)
White	193 (34.0)	165 (30.7)
Vaccinated in Current Season		
Yes	115 (20.3)	121 (22.5)
No	452 (79.7)	417 (77.5)
Influenza Vaccine Primed		
Yes	183 (32.3)	166 (30.9)
No	230 (40.6)	229 (42.6)
Unknown	154 (27.2)	143 (26.6)
Comorbidities Present[a]		
Asthma	93 (16.4)	100 (18.6)
Asthma within 90 Days[b]	21 (3.7)	40 (7.4)
Cystic Fibrosis	0 (0)	0 (0)
Congenital Anomalies	78 (13.8)	93 (17.3)
Diabetes Mellitus	1 (0.2)	5 (0.9)
Chronic Otitis Media	4 (0.7)	6 (1.1)
Renal Disorders	1 (0.2)	4 (0.7)
Hepatic Disorders	8 (1.4)	8 (1.5)
Neurological/Neuromuscular Disorders	10 (1.8)	18 (3.3)
Other Metabolic Disorders	14 (2.5)	25 (4.6)
History of Prematurity (<32 weeks)	19 (3.4)	39 (7.2)
Number of Comorbidities		
None	381 (67.2)	326 (60.6)
1–2 Comorbidities	178 (31.4)	194 (36.1)
>2 Comorbidities	8 (1.4)	18 (3.3)
Influenza Type & RSV Co-Infection		
Influenza A only	486 (85.7)	462 (85.9)
Influenza A with RSV	1 (0.2)	14 (2.6)
Influenza B only	80 (14.1)	60 (11.2)
Influenza B with RSV	0 (0)	2 (0.4)
Specimen Collection		
Early (Prior to Jan 12, 2014)	261 (46.0)	280 (52.0)
Late (On or after Jan 12, 2014)	306 (54.0)	258 (48.0)

[a]Individual comorbidity categories are not mutually exclusive.
[b]"Asthma within 90 days" is a subset of the "Asthma" category.
RSV: respiratory syncytial virus.

Table 2. Clinical features of children with moderate-to-severe influenza at Kaiser Permanente Northern California, 2013–2014 influenza season.

Symptoms	<6 months, n = 33 (%)	≥6 to <36 months, n = 189 (%)	≥3 to <9 years, n = 177 (%)	≥9 to <18 years, n = 139 (%)
Criteria for inclusion in moderate - to - severe cohort[a]				
Fever >39°C	8 (24.2)	81 (42.9)	77 (43.5)	74 (53.2)
AOM	2 (6.1)	53 (28.0)	23 (13.0)	4 (2.9)
LRTI	27 (81.8)	121 (64.0)	110 (62.1)	82 (59.0)
Extra-pulmonary complications	1 (3.0)	17 (9.0)	10 (5.6)	6 (4.3)
Breakdown of criteria[b]				
Fever >39°C only	4 (12.1)	33 (17.5)	45 (25.4)	53 (38.1)
Fever >39°C + AOM only	0 (0)	6 (3.2)	5 (2.8)	0 (0)
Fever >39°C + LRTI only	4 (12.1)	28 (14.8)	24 (13.6)	16 (11.5)
Fever >39°C + extra-pulmonary complications only	0 (0)	6 (3.2)	1 (0.6)	0 (0)
LRTI only	22 (66.7)	61 (32.3)	75 (42.4)	60 (43.2)
AOM only	2 (6.1)	17 (9.0)	13 (7.3)	3 (2.2)
Extra-pulmonary complications only	0 (0)	4 (2.1)	3 (1.7)	1 (0.7)
AOM + LRTI only	0 (0)	22 (11.6)	4 (2.3)	1 (0.7)
AOM + extra-pulmonary complications only	0 (0)	0 (0)	0 (0)	0 (0)
LRTI + extra-pulmonary complications only	1 (3.0)	3 (1.6)	5 (2.8)	0 (0)
Fever >39°C + AOM + LRTI only	0 (0)	5 (2.6)	1 (0.6)	0 (0)
Fever >39°C + AOM + extra-pulmonary complications only	0 (0)	2 (1.1)	0 (0)	0 (0)
Fever >39°C + LRTI + extra-pulmonary complications only	0 (0)	1 (0.5)	1 (0.6)	5 (3.6)
AOM + LRTI + extra-pulmonary complications only	0 (0)	1 (0.5)	0 (0)	0 (0)

[a]Categories are not mutually exclusive and add up to more than total per column.
[b]Categories are mutually exclusive.
AOM: physician-confirmed acute otitis media; LRTI: physician-confirmed lower respiratory tract illness;
Extra-pulmonary complications: physician-diagnosed serious extra-pulmonary complications (such as myositis, encephalitis, seizures, or myocarditis).

upon a history of fever or measured fever of ≥38°C (lower than our threshold) and a cough with onset within the last 10 days without requiring laboratory confirmation of influenza. Further, the case must also have been hospitalized.[5] In contrast, despite testing many children each year for influenza, KPNC hospitalizes few of them. Therefore, the WHO case definition may underestimate the true burden of disease in similar settings.

As might be expected, there was an increased likelihood of being classified as having M-S influenza disease among those in the youngest ages, particularly those aged <36 months where 63.4% of children met the definition of having M-S influenza, with most being classified as M-S due to LRTI and/or fever >39°C. Our results are generally consistent with a prior study in Finland, with their study finding that 65.8% of children aged <36 months, and 41.5% of children aged 3 to 13 years had M-S influenza.[7] However, the Finnish study noted that fever (40%) and AOM (26%) were the most frequently observed symptoms in all ages, while LRTI was only diagnosed in 8% of their cohort.[7] The Finnish study prospectively recruited children with respiratory infections in the outpatient setting. Since parents were explicitly asked to return to clinic for every fever or respiratory infection, it is likely that fever was over represented when compared with our study where care may not have been sought unless their child was experiencing additional respiratory and/or more serious symptoms. A recent study done in an outpatient setting in Germany using the same influenza definition has suggested that refining the fever definition from >39°C to ≥40°C would better distinguish M-S influenza from mild.[8] Other studies of influenza severity have found that LRTI and extra-pulmonary complications are common underlying medical conditions in US children hospitalized for influenza.[10–13] Another recent global systematic review of randomized controlled trials on the use of oseltamivir for the treatment of influenza in children has also found that AOM was present in up to 40% of children aged <3 years and 20% in children aged 3–6 years.[14] The differences observed in clinical symptoms in the US versus European cohorts may at least in part be explained by differences in routine clinical practices. Nonetheless, along with our present

Table 3. Clinical outcomes among children with mild and moderate-to-severe influenza at Kaiser Permanente Northern California, 2013–2014 influenza season.

Healthcare Outcome	Mild, *n* = 567 (%)	Moderate-to-severe, *n* = 538 (%)	P-value
Hospitalization			<0.01
No	565 (99.6)	500 (92.9)	
Yes	2 (0.4)	38 (7.1)	
Intensive care unit admission			0.012
No	567 (100.0)	532 (98.9)	
Yes	0 (0)	6 (1.1)	
Receipt of antibiotics			<0.01
No	519 (91.5)	314 (58.4)	
Yes	48 (8.5)	224 (41.6)	
Receipt of antivirals			0.522
No	318 (56.1)	312 (58.0)	
Yes	249 (43.9)	226 (42.0)	
Emergency department visits			<0.01
None	510 (89.9)	397 (73.8)	
≥1 day	57 (10.1)	141 (26.2)	
Follow-up outpatient visits			<0.01
None	436 (76.9)	285 (53.0)	
≥1 visit	131 (23.1)	253 (47.0)	
C-reactive protein value measured			0.018
No	560 (98.8)	520 (96.7)	
Yes	7 (1.2)	18 (3.3)	
Oxygen therapy used			<0.01
No	566 (99.8)	525 (97.6)	
Yes	1 (0.2)	13 (2.4)	

study, these data suggest that LRTI, extra-pulmonary complications, and AOM may be important clinical symptoms to consider for classifying influenza severity.

In contrast, another study evaluated predictors of influenza disease severity in children and found that selected presenting symptoms such as dyspnea, tachycardia, or fatigue increased the odds of being hospitalized or an ICU visit, while chills, congestion, fever, headache, myalgia, or sore throat decreased the odds.[15] Their analyses, however, did not adjust for vaccination status (current nor prior), an important consideration since priming can attenuate influenza illness.[16] It will be important for future studies to continue refining the definition to better characterize influenza severity.

In our study, children aged <36 months who were classified as M-S were associated with a 9.0 times increased likelihood of receiving antibiotics, while children aged ≥3 years were at 3.1 to 5.6 times increased likelihood of receiving antibiotics. Because our definition of M-S influenza includes diseases such as AOM and LRTI (both of which were common diseases found in our cohort), this finding was not unexpected as antibiotics are often used to treat patients with a diagnosis of AOM and LRTI (though not required at KPNC), which may be true regardless of influenza infection status.

Our study found that children with M-S influenza were associated with an increased likelihood of having had an ED visit, except for children aged <6 months. One explanation may be that the parents of very young infants are more likely to seek ED care regardless of influenza disease severity. However, this population was small (n = 57) and additional studies will be needed to understand this observation.

We also found that children with M-S influenza aged ≥6 months were associated with an increased likelihood of having had any

Table 4. Risk for emergency department visits, follow-up outpatient visits, receipt of antibiotics, and receipt of antivirals among children with moderate-to-severe influenza at Kaiser Permanente Northern California, 2013–2014 influenza season.

Healthcare utilization[b]	Adjusted relative risk[a] (95% CI)			
	<6 months	≥6 to <36 months	≥3 to <9 years	≥9 to <18 years
Any emergency department visits				
Moderate-to-severe influenza	1.3 (0.5–3.3)	**2.5* (1.4–4.5)**	**2.6* (1.4–4.5)**	**2.8* (1.8–4.3)**
Female	2.2 (0.9–5.1)	1.4 (0.9–2.1)	0.9 (0.5–1.5)	0.8 (0.5–1.2)
Late PCR test	0.6 (0.2–1.3)	1.0 (0.7–1.6)	1.2 (0.7–2.1)	**2.3* (1.4–3.8)**
Comorbidities present	n/a	1.4 (0.9–2.1)	1.2 (0.7–2.0)	1.3 (0.9–2.0)
Vaccinated in current season	n/a	1.1 (0.7–1.7)	1.2 (0.6–2.4)	1.2 (0.7–2.2)
Vaccine primed	n/a	n/a	0.7 (0.4–1.3)	0.5 (0.3–1.0)
Any follow-up outpatient visits				
Moderate-to-severe influenza	– *Not modeled* –	**1.6* (1.2–2.2)**	**2.3* (1.7–3.3)**	**1.8* (1.3–2.6)**
Female		0.8 (0.7–1.1)	1.1 (0.8–1.5)	1.3 (0.9–1.8)
Late PCR test		0.95 (0.8–1.2)	1.3 (0.9–1.8)	1.1 (0.7–1.7)
Comorbidities present		**1.3* (1.01–1.6)**	1.1 (0.8–1.5)	**1.7* (1.2–2.3)**
Vaccinated in current season		1.2 (0.9–1.5)	1.3 (0.9–1.9)	1.2 (0.7–2.0)
Vaccine primed		n/a	0.9 (0.6–1.2)	0.9 (0.6–1.4)
Receipt of antibiotics	– *Not modeled* –			
Moderate-to-severe influenza		**9.0* (4.1–19.8)**	**5.6* (3.3–9.4)**	**3.1* (1.9–4.9)**
Female		1.1 (0.8–1.4)	1.3 (0.9–1.9)	1.0 (0.6–1.5)
Late PCR test		1.0 (0.7–1.3)	0.8 (0.6–1.1)	1.2 (0.8–1.8)
Comorbidities present		**1.5* (1.1–1.9)**	1.1 (0.8–1.5)	0.9 (0.6–1.4)
Vaccinated in current season		**1.3* (1.01–1.7)**	1.3 (0.9–2.0)	1.4 (0.7–2.6)
Vaccine primed		n/a	1.0 (0.7–1.4)	0.8 (0.4–1.4)
Receipt of antivirals				
Moderate-to-severe influenza	0.7 (0.4–1.2)	0.9 (0.7–1.3)	0.9 (0.7–1.1)	1.2 (0.99–1.5)
Female	1.4 (0.8–2.5)	0.9 (0.7–1.2)	0.9 (0.7–1.2)	1.0 (0.8–1.2)
Late PCR test	1.1 (0.6–2.1)	1.2 (0.9–1.6)	1.1 (0.8–1.4)	**1.4* (1.1–1.7)**
Comorbidities present	0.9 (0.5–1.7)	1.3 (0.95–1.7)	**1.3* (1.03–1.7)**	1.2 (0.95–1.4)
Vaccinated in current season	n/a	1.1 (0.8–1.5)	0.9 (0.6–1.3)	1.0 (0.8–1.4)
Vaccine primed	n/a	n/a	0.9 (0.7–1.2)	1.1 (0.8–1.4)

* Statistically significant at α = 0.05.
[a]Models were run for each individual outcome and by age group (i.e., no combined analyses of all ages).
[b]Reference categories for each model: Mild influenza severity, male, early PCR test, early PCR test, no comorbidities present, not vaccinated in the current season, not vaccinated in prior season.
PCR: polymerase chain reaction.

outpatient follow-up visits after their positive PCR test. We found that children aged ≥6 to <36 months and those aged ≥9 to <18 years with any outpatient visits had an increased likelihood of having comorbidities. To further refine the M-S definition, it will be important for future studies to distinguish whether children with more outpatient visits are seeking care due to comorbidities (as opposed to influenza), or if the outpatient visits are for influenza-related complications.

We did not find an increased likelihood of being prescribed antivirals among children with M-S compared with mild influenza, although children aged ≥3 to <9 years with M-S influenza had a slight increased likelihood of having comorbidities. Because antivirals are most useful when prescribed within the first 2 days of symptoms,[17] it is possible that those with M-S influenza were beyond the time window during which antivirals would have been effective. Another explanation could be that because KPNC practice is to prescribe antiviral therapy to individuals suspected to have influenza regardless of severity, resulting in relatively high proportions receiving treatment (42–44% in our study), our study was unable to detect differences between mild and M-S cases. While children aged ≥9 to <18 years with M-S influenza were not at increased likelihood of receiving antivirals, they were at increased risk of having been diagnosed in the second half of the influenza season. The reason for this is unclear, but it is possible that with the 2013–2014 influenza season, there were age-specific differences in influenza susceptibility and/or differences in transmission dynamics due to age-specific social networks and interactions.[18–20]

We did not find a significant association between influenza vaccination status and M-S or mild influenza disease. Studies have shown that influenza vaccination significantly reduces the risk of influenza illness and influenza-related death in children.[5,6,21] Using a similar M-S definition, one meta-analysis also reported that live attenuated influenza vaccines provided high efficacy against M-S and mild influenza in children >24 months when compared with placebo.[22] Thus, it is plausible that current (or prior) vaccination may have attenuated illness enough for mild cases who did not seek care (and thus, were not tested for influenza) such that we were unable to detect an effect of vaccination on influenza severity in our study population. Further, because our study only included children who sought care and had a positive PCR test, it is possible that we were only identifying a portion of the "breakthrough" mild influenza cases who received influenza vaccinations. It is also possible that vaccinated mild cases in our study might have been classified as M-S if they had not been vaccinated. Historically, vaccination rates for children aged <18 years at KPNC have been approximately 50% for the past several years. In comparison, vaccine coverage in our study population during the 2013–2014 influenza season was relatively low (21.4%), supporting the idea that influenza vaccination may have averted or attenuated illness.

Our study had limitations. We only evaluated a single influenza season. Therefore, given the drifting nature of influenza viruses and changes in population immunity depending on the circulating strain, it is possible that our findings may not be generalizable beyond the 2013–2014 influenza season. Due to limited data, we also did not have adequate power to assess for associations between clinical severity and several outcomes. Because influenza varies from season to season, the proportion classified as having M-S disease may also vary depending on the type of influenza that is predominately circulating each season. To more fully evaluate the utility of the M-S measure, we would need to include multiple influenza seasons. Due to the relatively small sample size of 1,105 PCR positive children from one influenza season, we were also unable to include all covariates that we defined *a priori* to be biologically plausible and thought to be associated with influenza severity. For example, we were only able to assess co-infections with RSV, which was present in only 1.4% of our study cohort. Among those who did seek care, it is possible that co-infections with other bacterial and/or viral infections would have exacerbated a patient's symptoms and likelihood of seeking care. Because we did not assess co-infections other than RSV, it is possible that other types of co-infections might have influenced a patient's clinical diagnosis. In addition, there may have been selection bias, as we only included individuals who sought care, underwent testing for influenza, and who tested positive. These individuals may have different healthcare-seeking patterns than those who did not seek care. For example, those who seek care may also be more likely to have used antipyretics, and antipyretic use may confound the relationship between fever >39°C (one of our M-S criteria) and the setting in which one may seek care. For example, individuals who more proactively use antipyretics at the first sign of illness may also be more likely to seek immediate care in the ED setting, which could lead to an underestimation of M-S cases in the ED setting. Approximately 28% of our study population were not members for the whole study period, which may have also limited our ability to detect a significant priming effect. We also did not independently verify the completeness or accuracy of ICD-9 codes (as coded by the treating pediatrician) captured in the patient's electronic medical record. As a result, it is possible that missing codes or ascertainment bias of symptoms may have led to an underestimate of the number of M-S cases. Further, we did not evaluate severe disease using other case definitions such as the one used by the WHO. As the WHO definition is broader and does not require a positive influenza result, use of this case definition that relies on clinical diagnoses and requires hospitalization would have likely underestimated the influenza burden and eliminated the ability to detect and categorize influenza severity outside of the hospital setting. Finally, it is possible that we could have seen similar findings among those who tested negative for influenza. Future studies should also evaluate PCR test-negative individuals to assess the validity and sensitivity of our severity definition.

In conclusion, children who were classified as having moderate-to-severe influenza had an increased likelihood of receiving antibiotics, having ED visits, and having follow-up outpatient visits, particularly among children aged ≥6 to <36 months (Figure 1). We may have some ability to differentiate children with more clinically severe disease, but prospective studies are needed to validate the utility of this definition. Better distinguishing mild from clinically significant influenza disease could help improve influenza vaccines by better assessing how well they protect against a range of disease severity. Studies that include additional influenza seasons and children who tested negative for influenza may be needed to better understand how well the moderate-to-severe influenza definition is associated with influenza disease severity in children.

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Disclosure of Potential Conflicts of Interest

P. Buck, E. Yanni, R. Bekkat-Berkani, and A. Schuind are employees of the GSK group of companies. P. Buck, A. Schuind, E. Yanni, and R. Bekkat-Berkani hold shares in the GSK group of companies. N.P. Klein has received research grant support from the GSK group of companies, Sanofi Pasteur, Novartis, Merck, MedImmune, Pfizer, and Protein Sciences. A. Hsiao, A. Yee, J. Hansen, E.M. Lewis, and L. Aukes have no conflicts of interest.

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Appendix A1. ICD-9 codes for specification of symptoms for moderate-to-severe influenza*

M-S category	ICD-9 codes included
Physician-confirmed acute otitis media (AOM)	380.10, 382.11, 382.01, 382.02, 382.4, 382.9†
Physician-confirmed lower respiratory tract illness (LRTI)‡	165.0, 464.1, 464.10, 464.11, 464.2, 464.20, 464.21, 464.4, 466, 466.0, 466.1, 466.11, 466.19, 480.0, 480.1, 480.2, 480.3, 480.8, 480.9, 481, 482.0, 482.1, 482.2, 482.3, 482.30, 482.31, 482.32, 482.39, 482.4, 482.40, 482.41, 482.42, 482.49, 482.8, 482.81, 482.82, 482.83, 482.84, 482.89, 482.9, 483, 483.0, 483.1, 483.8, 484.1, 484.3, 484.5, 484.6, 484.7, 484.8, 485, 486, 487.0, 487.1, 487.8, 488.01, 488.02, 488.09, 488.11, 488.12, 488.81, 490, 518.0, 518.1, 518.2, 518.82, 519.11, 519.8, 786.0, 786.05, 786.07, 786.09, 786.1, 786.2, 786.6, 786.7
Physician-confirmed serious extra-pulmonary complications	729.1, 008.8, 070.9, 322, 322.0, 322.1, 322.2, 322.9, 323, 323.0, 323.01, 323.02, 323.1, 323.2, 323.4, 323.41, 323.42, 323.5, 323.51, 323.52, 323.6, 323.61, 323.62, 323.63, 323.7, 323.71, 323.72, 323.8, 323.81, 323.82, 323.9, 345, 345.0, 345.00, 345.01, 345.1, 345.10, 345.11, 345.2, 345.3, 345.4, 345.40, 345.41, 345.5, 345.50, 345.51, 345.60, 345.61, 345.7, 345.70, 345.71, 345.8, 345.80, 345.81, 345.9, 345.90, 345.91, 420, 420.0, 420.9, 420.90, 420.91, 420.99, 421, 421.0, 421.1, 421.9, 422, 422.0, 422.9, 422.90, 422.91, 422.92, 422.93, 422.99, 425, 425.0, 425.1, 425.2, 425.3, 425.4, 425.5, 425.7, 425.8, 425.9, 780.31, 780.32, 780.39

* All general terms for each criteria (i.e., LRTI: shortness of breath, pulmonary congestion, pneumonia, bronchiolitis, bronchitis, wheezing, or croup; extra-pulmonary complications: myositis, encephalitis, seizure, or myocarditis) were cross-checked with ICD-9 codes and the Centers for Disease Control and Prevention's High-Risk Inpatient Influenza Vaccination Module.

† Patient must have 382.9 code in addition to KP diagnosis descriptions that indicate acute (as opposed to chronic) otitis media.

‡ Patient must have 487.1 code in addition to KP diagnosis description of "Influenza with other respiratory manifestations"; patients with 487.1 and KP diagnosis descriptions of "Influenza-like illness" or "Influenza" were classified as having mild influenza.

ICD-9: International Classification of Diseases, Ninth Revision.

Appendix A2. Antibiotic classes and antiviral neuraminidase inhibitors

Antibiotics – pharmacy class (systemic only; does not include topical eye, ear, nose, etc.)	• Absorbable sulfonamides • Aminocyclitols • Aminoglycosides • Antileprotics • Anti-mycobacterium agents • Antiprotozoal • Antitubercular antibiotics • Betalactams • Carbapenems (thienamycins) • Cephalosporins – 1st, 2nd, 3rd, 4th, 5th generations • Chemotherapeutics, antibacterial, misc. • Chloramphenicol • Cyclic lipopeptides • Glycylcyclines • Ketolide • Lincosamides • Lipoglycopeptide antibiotics • Macrolide combination • Macrolides • Nitrofuran derivatives • Oxazolidinones • Penicillins • Polymyxin and derivatives • Quinolones • Rifamycins and related derivative antibiotics • Streptogramins • Tetracyclines • Vancomycin and derivatives
Antivirals – neuraminidase inhibitors	• Oseltamivir • Peramivir • Zanamavir

Appendix A3. ICD-9 codes for specification of comorbidities

Comorbid category	ICD-9 codes included[a]
Cystic fibrosis	277.0
Asthma	493[b]
Congenital abnormalities (including cardiovascular and pulmonary defects)	741, 742, 744, 745, 746, 747, 748, 749, 750, 751, 753, 756, 757, 758, 759
Diabetes mellitus	250
Chronic otitis media[c]	382.1, 382.2, 382.3, 382.9[c]
Renal disorders	581, 582, 583, 584, 585, 586, 587, 588, 589
Hepatic disorders	570, 571.4, 571.5, 571.6, 571.8, 571.9, 572, 573, 576, 579.0, 579.8, 579.9
Neurological or neuromuscular disorders	320[d], 321[d], 322[d], 323[d], 324[d], 325[d], 326, 330, 331, 333, 334, 335, 336, 337, 340, 341, 342, 343, 344, 345[d], 347, 348[d], 349, 356, 357, 358, 359
Other metabolic disorders	270, 271, 272, 273, 275, 276.2[d], 278.01, 279
History of prematurity	765.21, 765.22, 765.23, 765.24, 765.25, 765.26, 765.27, 765.28

[a]All ICD-9 subcodes were generally included; in some instances as with Hepatic Disorders, only specific subcodes were used indicated in the table.
[b]Asthma must be diagnosed within 2 years of the specimen collection date; we also separately characterized asthma diagnosed within 90 days of specimen collection date.
[c]Patient must have 382.9 code in addition to KP diagnosis descriptions that indicate chronic (as opposed to acute) otitis media.
[d]A 90-day washout period applies to these codes.
ICD-9: International Classification of Diseases, Ninth Revision.