

Diagnostic uncertainty of herpangina and hand-foot-and-mouth disease and its impact on national enterovirus syndromic monitoring

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SUMMARY

Community burden of enterovirus is often monitored through syndromic monitoring systems based on reported cases of enterovirus-related diagnoses (EVI). The extent to which this is affected by under- and over-diagnosis has not been reported. In Taiwan, children often make more than one health care visit during an episode of infection. We used change of diagnosis within an episode of infection as a guide of diagnostic uncertainty among a nationally representative cohort of Taiwanese children (n=13,284) followed from birth to the 9th birthday through electronic health records. We conducted a nested case-control analysis and estimated cross-diagnosis ratios (CDRs) as the observed proportion of ARI diagnoses following an EVI diagnosis in excess of background ARI burdens. With 19,357 EVI diagnoses in this cohort, the CDR within 7 days was 1.51 (95% CI 1.45-1.57), confirming a significant excess of ARI diagnoses within the week following an EVI diagnosis. We used age-specific CDRs to calibrate weekly EVI burdens among children aged 3-5 years in 2008, and the difference between observed and calibrated weekly EVI burdens was small. Therefore, there was evidence suggesting a small uncertainty in EVI diagnosis, but the observed EVI burdens through syndromic surveillance were not substantially affected by the small uncertainty.

INTRODUCTION

Enteroviral infections are common in early childhood.[1-4] Although the majority of infections are self-limited, some subtypes are associated with life-debilitating consequences such as meningitis, encephalitis, or cardiomyopathy, and have posed major public health threats in Asia [5-9] while potentially emerging in other countries.[10, 11] National intelligence of circulating enterovirus in many countries has relied primarily on laboratory-based surveillance. In Asian countries where burdens of enterovirus to the healthcare system are high and require immediate responses, these burdens are additionally monitored through syndromic reports of cases with enterovirus-associated diagnoses, mostly herpangina and hand-foot-and-mouth disease.[1-4] However, overlapping presentations are common between enterovirus-related diagnoses (EVIs) and acute respiratory infections (ARIs),[12] and the monitored syndromic burden of EVI may be affected by over- or under-diagnosis of EVI. The extent of this effect has not been investigated.

In Taiwan, diagnoses of primary and secondary health care visits are routinely recorded electronically and stored centrally. These diagnostic records are rich data sources to identify childhood infectious diagnoses, and are used as a tool for real-time monitoring of enteroviral trends.[2] With high accessibility of medical care among young children, a large proportion of young children visit physicians several times during a course of infection. Discrepancies of diagnoses during several visits of an infectious episode can be used to assess the degree of diagnostic uncertainty in this episode. A high degree of uncertainty may indicate poor accuracy in EVI diagnosis that may affect the precision of enterovirus syndromic monitoring system. In this study, we estimate the extent to which monitored burdens of EVIs through syndromic monitoring system might be affected by cross-diagnosis between ARIs and EVIs.

METHODS

Complete ambulatory care medical history of 13,284 Taiwanese children born in 2000 were followed from birth to their 9th birthday through the Taiwan Longitudinal National Health Insurance Research Dataset 2005.[13] Briefly, this is a nationally representative, random and anonymous sample of 1 million people of the Taiwanese population in 2005 from the National Health Insurance Database which covered >99% of Taiwanese population. In this database, primary diagnoses of all medical visits were recorded in this database according to the International Classification of Diseases, 9th Revision (ICD-9) since 2000, allowing consistent coding criteria to identify of diagnosis of ARI (ICD-9 460-466) and EVI (ICD-9 074.0,074.3) during the follow up of this birth cohort. For ARI we included most minor acute respiratory illness such as acute pharyngitis, acute sinusitis, etc, which can be caused by any virus, including enteroviruses. For EVI we included herpangina (074.0) and hand-foot-and-mouth disease (074.3) to be consistent with the enterovirus syndromic monitoring system in Taiwan. Therefore, wherever EVI is referred to the species associated with severe consequences were implied.

We calculated the incidence of ARI and EVI by week of age from birth to the 9th birthday in this cohort born in 2000. To examine any findings specific to birth cohort, we also compared the incidence to another cohort born in 2003 from the same data source and extraction method from birth to the 6th birthday.

Nested case-control analysis

Because any ARI diagnosis after EVI could simply reflect the higher background incidence of ARI compared to the background incidence of EVI, we conducted a nested case-control study to test whether there were occurrences of ARI after EVI in excess of the background incidence of ARI. The case-control study was nested in the original cohort (born in 2000) to

compare occurrences of ARI diagnoses following a case-date and a control-date. Children of the same sex and born in the same week and the same region (Northern, Central, Southern, Eastern, and others) [13] were selected into comparison groups. Occurrences of ARI diagnoses following the dates on which a child had an EVI diagnosis (case-dates) were compared to the occurrences of ARI diagnoses following the same dates of other children (control-dates) in the same comparison group. Dates with EVI diagnoses in the past 7 days, or on which there was an ARI diagnosis were excluded from analyses. Diagnostic uncertainty of EVI was quantified in terms of cross-diagnosis ratios (CDRs) using conditional logistic regression (SAS 9.4) as the relative risk of case-dates versus control-dates of the proportions of ARI diagnosis following the date, stratified by comparison group and index date. Therefore, children contributed to case-dates on the dates they had an EVI diagnosis, and contributed to control-dates on the dates other children in the same comparison group had an EVI diagnosis.

We calculated CDRs 1-7, 8-14, 15-21, and 22-28 days following the index date. A CDR larger than 1.0 within a short period following an index date suggested that children with an EVI diagnosis were given ARI diagnoses more often than expected according to the background ARI burdens after the EVI diagnosis, and may indicate some episodes of ARI were diagnosed as EVI in the first visit of the infectious episode. By contrast, a CDR larger than 1.0 within a longer period may indicate existence of other long-term factors of excessive ARI diagnosis, such as high medical accessibility or environment with high circulating virus among those who were diagnosed with EVI.

Chi-squared tests were used for heterogeneity of CDRs across different subgroups or conditions, including sex (boys and girls), age (0-2, 3-5, and 6-8 years), season (in four three-month periods starting from December), and the burden of ARI and EVI in the prior week in quartiles, calculated from the Taiwan Longitudinal National Health Insurance Research

Dataset 2005. Because all children in this dataset were born in or before 2005 and were age 4 years or older by the end of year 2009, we used the total number of ARI or EVI diagnoses among children aged 4-6 years to represent prior-week ARI and EVI burdens.

We also used conditioned CDRs to calculate the population attributable fraction [14] of ARI that could have been cross-diagnosed as EVI, and calibrated the observed weekly EVI burdens by subtracting the numbers of cross-diagnosed cases in the week.

RESULTS

Characteristics of children in this cohort are shown in Table 1. There were 1,486,926 ARI diagnoses in this cohort before the 9th birthday (112 ARI per child on average), compared to only 19,357 EVI diagnoses (1.5 per child). The burden of ARI and EVI varied substantially with age. Figure 1A-B shows the proportion of children who had ARI or EVI at each week of age from birth to their 9th birthday (in fine dots), plotted against five-week moving averages (solid lines). We observed two age peaks of ARI, around the first and the fifth birthday. Two age peaks were also observed for EVI, at around the second and the fifth birthday. Due to viral seasonality, these age peaks varied slightly according to time of the year the children were born (Appendix P2). The gap between two peaks coincided with the outbreak of Severe Acute Respiratory Syndrome (SARS) in 2002-2003, during which health visits declined substantially, as reported previously.[13] We examined the burdens among another cohort of 9383 children born in 2003 (Figure 1C-D). The burden of ARI by week of age was substantially lower in this cohort, and the peak at around age 5 was less obvious. By contrast, the burden of EVI by week of age was similar between the two cohorts.

Diagnosis of ARI was common following an EVI diagnosis

The proportions of having the same or different diagnosis within 28 days following a previous health care visit are shown by three age groups (year 0-2, 3-5, 6-8) in Figure 2. For both ARI and EVI diagnoses, the proportion of having a second visit with the same diagnosis was generally lower among older age groups, but there was qualitative difference between ARI and EVI: unlike ARI for which substantial proportion of same diagnosis consistently occurred throughout 1-28 days after the initial diagnosis (Figure 2A), most repeated diagnoses for EVI occurred within 7 days (Figure 2B). Across all age groups, the proportions of having an EVI diagnosis following an ARI diagnosis other diagnoses was very low ($\leq 2\%$ within 28 days, Figure 2C). By contrast, there were substantial proportions of children diagnosed to have ARI within 7 days following an EVI diagnosis (16-28%, Figure 2D).

These findings confirmed our speculation that there was indeed high background incidence of ARI in this population, and any ARI occurrence after EVI could be largely contributed by the background incidence of ARI. It would be necessary to use a nested case-control design to investigate whether there was ARI incidence after EVI in excess of the background incidence of ARI (see below).

The proportion of ARI diagnoses following an EVI diagnosis was in excess of background ARI burdens

Using the nested case-control approach, we observed excessive ARI diagnoses 1-7 days after an EVI diagnosis (CDR=1.67, 95%CI 1.61-1.74). Excessive ARI diagnoses were also observed 8-14, 15-21, and 22-28 days following an EVI diagnosis, although the CDRs were substantially smaller (Table 2, left column). We further adjusted the CDRs for the total number of ARI diagnoses each child had at age 1, 4 and 7 years as a general tendency of having an ARI diagnoses. The CDR 1-7 day after an EVI diagnosis was attenuated after

adjustment (CDR=1.51, 95%CI 1.45-1.57), and so were the CDRs 8-14, 15-21, and 22-28 days after (Table 2, right column).

The adjusted CDRs did not vary with sex, but did vary with characteristics that may affect an accurate EVI diagnosis (Table 3). Adjusted CDRs were higher among older (age 6-8 years) and younger (age 0-2 years) ages compared to the age when disease presentation was considered typical (age 3-5 years, p for heterogeneity<0.0001). Adjusted CDRs were also found highest in summer (June, July, and August). We then stratified the analyses by community burdens of ARI and of EVI in the prior week. The Spearman correlation between burdens of ARI and EVI in the same week was -0.11, $p=0.01$ (522 weeks in total). High adjusted CDRs were found to be associated more strongly with lower (compared to higher) ARI weekly burdens, and less strongly with lower (compared to higher) EVI weekly burdens (p for heterogeneity = 0.0002 for ARI and 0.03 for EVI).

Cross-diagnosis between ARI and EVI did not substantially affect enterovirus syndromic monitoring system

To quantify the extent to which observed burdens of EVIs may be inflated by over-diagnosis, we calculated CDRs specific to age and prior-week ARI burdens, and used the CDRs to calculate population attributable fractions of ARI that could have been over-diagnosed as EVI, and then used this fraction to calculate numbers of over-diagnosed EVI (Appendix P3). As a visual example, we plotted the observed weekly EVI burden for age 3-5 years in 2008 against the calibrated weekly burdens. As shown in Figure 3, the difference between observed and calibrated weekly EVI burdens was small.

DISCUSSION

In this national representative birth cohort in Taiwan based on routinely collected diagnostic information from primary and secondary health care databases, we investigated the extent to which enterovirus syndromic monitoring system may have been affected by diagnostic uncertainty of EVI. Because it was not possible to verify each diagnosis, we assumed that excessive ARI diagnoses following an EVI diagnosis, if there were, were due to ARI being over-diagnosed as EVI at the first visit. We quantified these excessive ARI diagnoses in terms of CDRs as a guide of EVI over-diagnosis, and used CDRs to calibrate syndromic monitoring observations. Our analyses confirmed that there were excessive ARI diagnoses following an EVI diagnosis, but the observed burdens of enterovirus was not substantially affected.

Age and seasonality are major factors of ARI and EVI, and this is mostly demonstrated in cross-sectional studies.[3, 4, 15, 16] In this study we followed each child's complete medical history from birth to the 9th birthday among a large and nationally representative sample of Taiwanese children, and summarised the actual trajectory of ARI and EVI. We were able to compare the trajectory with that of another cohort born in 2003, and the cohort difference of EVI was small. We also demonstrated that most repeated EVI diagnoses in this cohort occurred within 7 days following the previous one, consistent with the natural disease course.[16] Altogether with the finding that observed enteroviral burdens based on EVI diagnosis was not affected substantially by diagnostic uncertainty, our results suggest good credibility in this enterovirus syndromic monitoring system.

One major limitation of this study is residual confounding. Although we have adjusted for number of ARI diagnosis at age 1, 4, and 7 years, the excessive ARI diagnosis following an EVI diagnosis could still be confounded by residual effect of medical accessibility or health-seeking tendency, or by other confounding factors. The diagnostic criteria for ARI and for EVI may vary by case, by season, or by diagnosing physician. Cases and controls were matched by week of birth, sex, and region, but we could not exclude the possibility that children who had EVI were more susceptible to other infections or were in an environment where ARI more likely occurred. Nevertheless, the low CDRs after 7 days after adjustment, compared to those within 1-7 days, could suggest that any residual confounding is relatively small.

We did not quantify the proportion of EVI under-diagnosis. Because the proportion of EVI diagnoses following an ARI diagnosis was very small within 7 days, the risk of under-diagnosis in this population is relatively small. We also did not quantify the proportion of EVI over- or under- diagnosis related to cross-diagnosis with other diseases. Because these diseases do not cause a size of burden comparable to ARI, the risk of inflation or deflation caused by these cross-diagnoses may also be small.

Although the study cannot explicitly account for all sources of diagnostic uncertainty, the approach is comparable to using repeated measurements to assess reproducibility regardless of the source of errors. The syndromic monitoring system for enterovirus infections in Taiwan takes the advantage of real-time registration of genuine clinical impressions from the clinical settings, but the reliability inevitably relies on general consensus of diagnostic criteria among physicians across the country. Deviation from this general consensus could be a source of confounding or diagnostic uncertainty. Syndromic monitoring, as it is named, uses

one or more enterovirus-related diagnoses as indicators of healthcare burden attributed to enterovirus. Because presentations of enteroviruses could depend on various viral and host factors such as viral subtypes, host age, or immune status, the syndromic monitoring may not always reflect this variation and be prone to errors. We used the nested case-control study design, and observed a small effect of diagnostic inconsistencies on the estimated burden of enteroviruses based on syndromic monitoring.

The heterogeneity between CDRs has suggested some host or environmental factors that had contributed to diagnostic uncertainty. The higher CDRs among younger and older children may suggest difficulties in diagnosing EVI among these ages, perhaps due to non-specific presentations and difficulties in differential diagnosis. The higher CDRs associated with summer season, low prior-week ARI or EVI burden may affect children's exposure history, health care seeking tendency, or physician's diagnostic preference. Our findings suggest these factors, wherever accountable in our analyses, may not substantially affect our observation of EVI burdens at the population level in Taiwan. To which extent these factors affect individual EVI diagnosis is unclear. To which extent our findings can be generalised to other population requires further investigation.

FINANCIAL SUPPORT

The study did not receive external funding.

CONFLICT OF INTEREST

All authors declared no conflict of interest.

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ETHICAL STANDARDS

The study does not involve human or animal experimentation

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Table 1. Characteristics of the study cohort and diagnoses

All children n=13,249		
Sex		
Boys	6972	
Girls	6277	
Region		
Northern	6396	
Central	2516	
Southern	3690	
East	548	
Other territories or unknown	99	
Season of birth		
Winter (Dec-Feb)	3124	
Spring (Mar-May)	3225	
Summer (Jun-Aug)	3186	
Autumn (Sep-Nov)	3714	
	ARI diagnoses n=1486926	EVI diagnoses n=19357
By sex*		
Boys	804759	10521
Girls	682080	8832
By age		
Year 0-2	622477	9952
Year 3-5	594114	7564
Year 6-8	270335	1841
By season		
Winter (Dec-Feb)	412454	2228
Spring (Mar-May)	391911	6096
Summer (Jun-Aug)	300773	6609
Autumn (Sep-Nov)	381788	4424
Diagnoses given in the following 7 days		
Any diagnosis	854971	11938
ARI diagnosis	708843	4868
EVI diagnosis	8284	6268

*Sex information is missing in <0.1% of diagnoses. Information was obtained from other episodes of the same child in further analyses
 ARI: acute respiratory infections; EVI: enterovirus-related diagnosis, including herpangina and hand-foot-and-mouth disease.

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Table 2 Cross-diagnosis ratios by duration after the first enterovirus-related diagnosis

Duration after the first EVI diagnosis	Unadjusted	Adjusted for tendency to
	CDR (95% CI)	have ARI diagnosis CDR (95% CI)
1-7 days	1.67 (1.61-1.74)	1.51 (1.45-1.57)
8-14 days	1.28 (1.23-1.33)	1.14 (1.09-1.18)
15-21 days	1.30 (1.24-1.35)	1.15 (1.10-1.20)
22-28 days	1.36 (1.30-1.41)	1.21 (1.16-1.26)

Case and control dates were matched by week of birth, sex, and region. Cross-diagnostic ratios (CDRs) and 95% confidence intervals (CIs) were estimated using conditional logistic regression. Tendency to have ARI diagnosis is indicated by total numbers of acute respiratory infections in the year of age 1, 4, and 7 years of each child. ARI: acute respiratory infections; EVI: enterovirus-related diagnosis, including herpangina and hand-foot-and-mouth disease.

Table 3 Cross-diagnosis ratios by age, season, and community burden of ARI or EVI in the prior week

	Number of EVI diagnoses	7 day cross-diagnosis ratio (CDR, 95% confidence interval)
Overall	10789	1.51 (1.45-1.57)
By sex		
Boys	5772	1.52 (1.44-1.61)
Girls	5015	1.49 (1.40-1.58)
		p for heterogeneity=0.63
By age		
Year 0-2	6004	1.60 (1.51-1.69)
Year 3-5	4283	1.22 (1.14-1.30)
Year 6-8	502	1.84 (1.58-2.14)
		p for heterogeneity <0.0001
By season		
Winter (Dec-Feb)	1497	1.50 (1.34-1.68)
Spring (Mar-May)	3456	1.49 (1.39-1.60)
Summer (Jun-Aug)	3141	1.68 (1.57-1.81)
Autumn (Sep-Nov)	2695	1.31 (1.20-1.42)
		p for heterogeneity=0.0002
By community ARI burden in the prior week		
1st-25th percentile	682	1.78 (1.56-2.04)
26th-50th percentile	1944	1.68 (1.53-1.83)
51st-75th percentile	4738	1.44 (1.35-1.53)
76th-100th percentile	3425	1.41 (1.30-1.52)
		p for heterogeneity=0.0009
By community EVI burden in the prior week		
1st-25th percentile	1069	1.81 (1.59-2.06)
26th-50th percentile	1741	1.47 (1.32-1.63)
51st-75th percentile	2408	1.49 (1.37-1.62)
76th-100th percentile	5571	1.47 (1.39-1.56)
		p for heterogeneity=0.03

Case and control dates were matched by week of birth, sex, and region. Cross-diagnostic ratios (CDRs) and 95% confidence intervals (CIs) were estimated using conditional logistic regression, adjusted for total numbers of acute respiratory infections at age 1, 4, and 7 years. ARI: acute respiratory infections; EVI: enterovirus-related diagnosis, including herpangina and hand-foot-and-mouth disease.

FIGURE LEGENDS

Figure 1

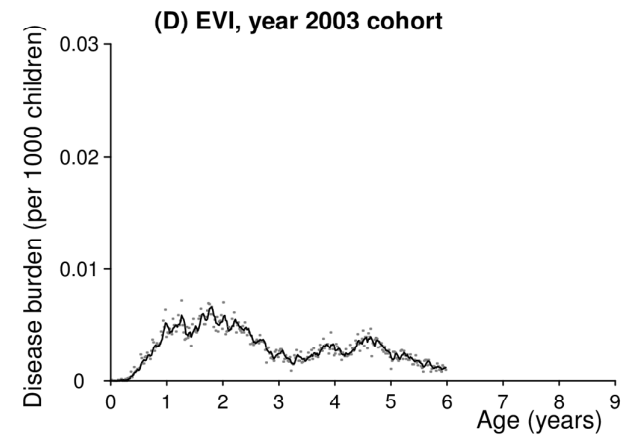
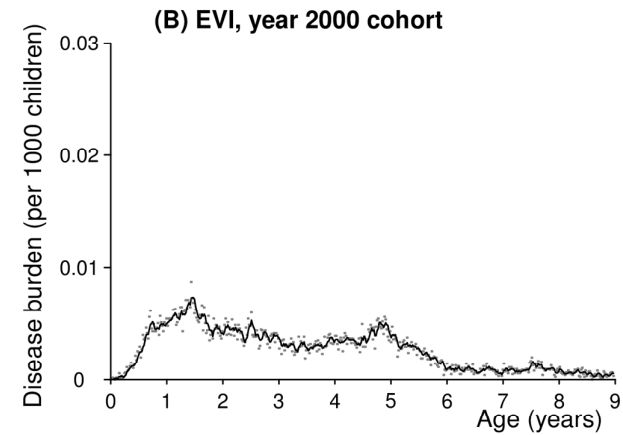
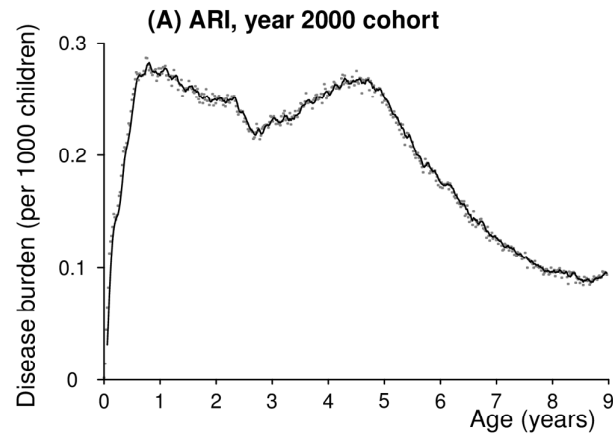
Disease burdens (dots) and 5-week moving average (lines) of acute respiratory infections (ARI) and enterovirus-related diagnoses (EVI) by week of age in the study cohort born in 2000 from birth to the 9th birthday (Figure 1A&B) and in a comparison cohort born in 2003 followed from birth to the 6th birthday (Figure 1C&D)

Figure 2

Cumulative proportions of having an acute respiratory infection (ARI) or enterovirus-related diagnoses (EVI) diagnosis within 28 days following a previous same diagnosis (Figure 2A&B) and following the other diagnosis (Figure 2C&D) in three age groups

Figure 3

Observed burdens of acute respiratory infections (ARI, upper half) and observed (black) and calibrated (grey) burden of enterovirus-related diagnoses (EVI, lower half) in 2008 among children aged 3-5 years in Taiwan, in weekly burdens (dots) and 5-year moving averages (lines).



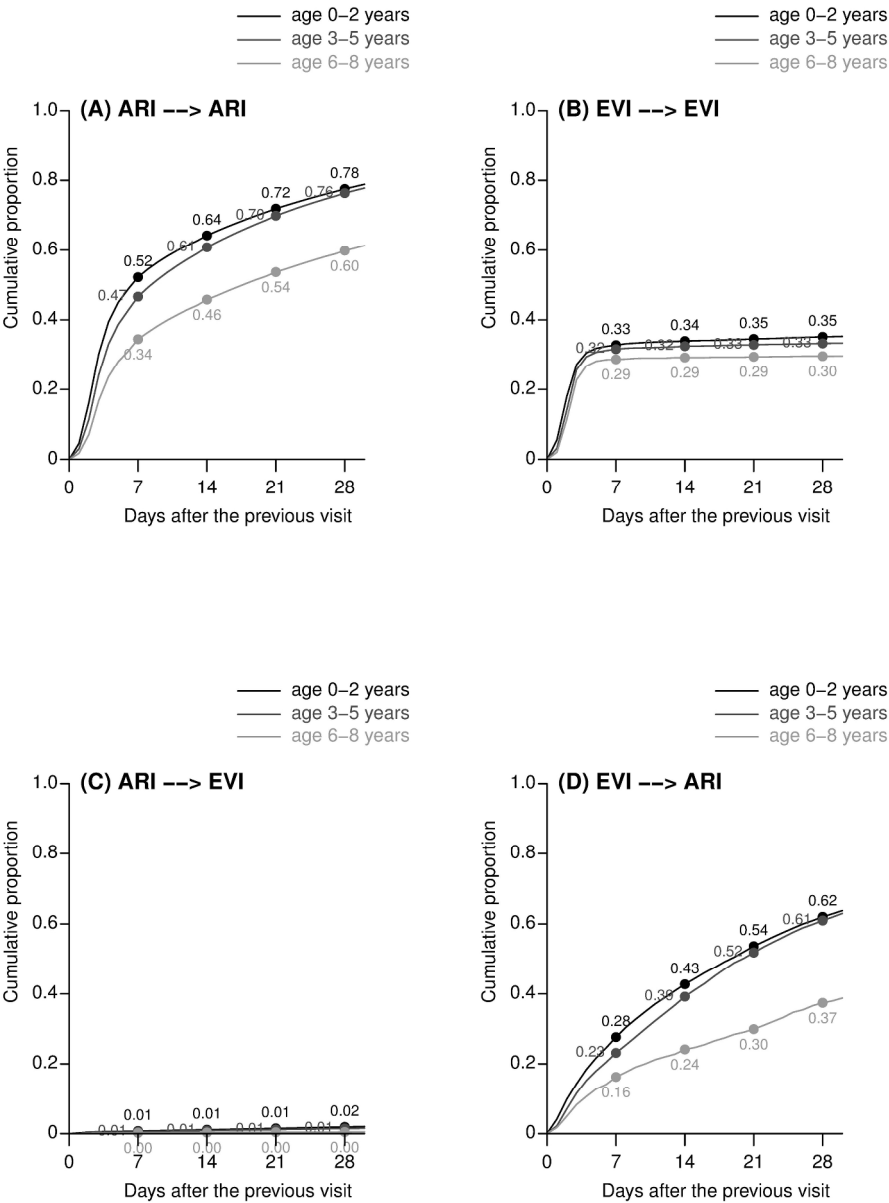


Figure 2
Cumulative proportions of having an acute respiratory infection (ARI) or enterovirus-related diagnoses (EVI) within 28 days following a previous same diagnosis (Figure 2A&B) and following the other diagnosis (Figure 2C&D) in three age groups

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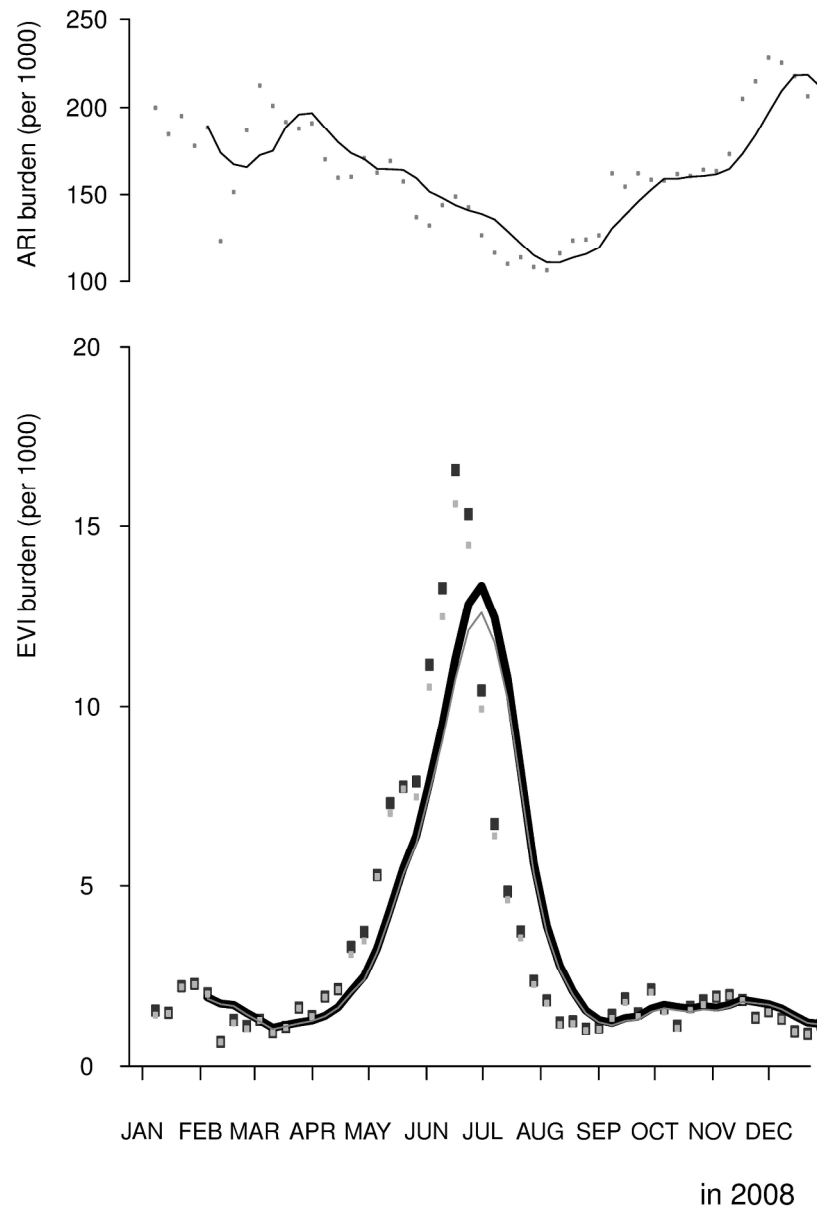


Figure 3

Observed burdens of acute respiratory infections (ARI, upper half) and observed (black) and calibrated (grey) burden of enterovirus-related diagnoses (EVI, lower half) in 2008 among children aged 3-5 years in Taiwan, in weekly burdens (dots) and 5-year moving averages (lines).

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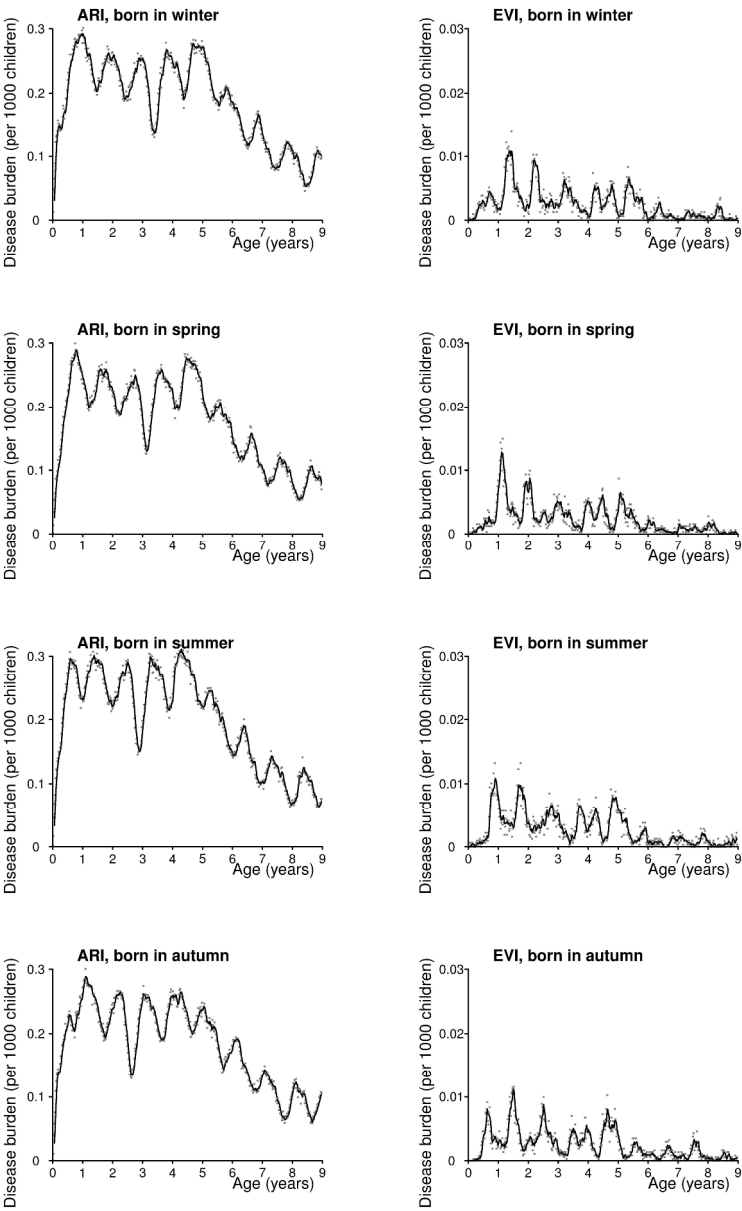
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APPENDIX

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P2. Disease burdens (dots) and 5-week moving average (lines) of acute respiratory infections (ARI) and enterovirus-related diagnoses (EVI) by week of age in the study cohort born in 2000 by season of birth

P3 Inflation of weekly EVI burdens stratified by age, prior-week ARI burden, and current-week EVI burden. ARI: acute respiratory infections; CDR: cross-diagnostic ratios; CI: confidence interval; EVI: enterovirus-related diagnoses.



Appendix P2. Disease burdens (dots) and 5-week moving average (lines) of acute respiratory infections (ARI) and enterovirus-related diagnoses (EVI) by week of age in the study cohort born in 2000 by season of birth
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APPENDIX P3

		Number of EVI diagnoses	7 day cross- diagnosis ratio (CDR, 95% CI)	Assumed ARI incidence (per 1000)	Inflation of EVI burden (per 1000)			Inflation of EVI burden (%)					
					At EVI burden (per 1000)			At EVI incidence (per 1000)					
					5	10	15	5	10	15			
ARI Burden													
Age 0-2	1st-25th percentile	183	1.64 (1.24-2.17)	50	0.2	0.3	0.5	3.2%	3.2%	3.2%			
	26th-50th percentile	1200	1.74 (1.55-1.96)	100	0.4	0.7	1.1	7.4%	7.4%	7.3%			
	51st-75th percentile	2513	1.54 (1.42-1.68)	200	0.5	1.1	1.6	10.9%	10.8%	10.8%			
	76th-100th percentile	2108	1.58 (1.43-1.74)	300	0.9	1.7	2.6	17.3%	17.3%	17.2%			
Age 3-5	1st-25th percentile	225	1.42 (1.09-1.84)	50	0.1	0.2	0.3	2.1%	2.1%	2.1%			
	26th-50th percentile	565	1.39 (1.18-1.64)	100	0.2	0.4	0.6	3.9%	3.9%	3.9%			
	51st-75th percentile	2191	1.23 (1.12-1.35)	200	0.2	0.5	0.7	4.6%	4.6%	4.6%			
	76th-100th percentile	1302	1.05 (0.92-1.20)	300	0.1	0.1	0.2	1.5%	1.5%	1.5%			
Age 6-8	1st-25th percentile	274	2.05 (1.69-2.48)	50	0.3	0.5	0.8	5.2%	5.2%	5.2%			
	26th-50th percentile	179	1.58 (1.21-2.07)	100	0.3	0.6	0.9	5.8%	5.8%	5.8%			
	51st-75th percentile	34	1.49 (0.73-3.06)	200	0.5	1.0	1.5	9.8%	9.8%	9.8%			
	76th-100th percentile	15	1.43 (0.30-6.81)	300	0.6	1.3	1.9	13.0%	13.0%	12.9%			