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A coxsackievirus A2 herpangina outbreak in a kindergarten in Shenzhen, China: evidence chain from dispersed clinical labels to class-date clustering and VP1 confirmation

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Abstract

Background

Herpangina is a frequent enterovirus-associated illness in childhood, but it is not subject to statutory notification in China. In kindergartens, outbreak signals may first appear as dispersed clinical labels, non-specific symptoms, and illness-related absences rather than as formal disease reports. We investigated a coxsackievirus A2 (CV-A2) herpangina outbreak in a kindergarten in Shenzhen, China, to describe an evidence chain linking heterogeneous outpatient diagnoses, class-date clustering, and VP1-based etiological confirmation.

Methods

Operational case definitions were developed, and cases were searched using attendance lists, illness-related absence follow-up records, morning/noon health-check logs, interviews, and medical-visit information. Combined throat/anal swabs from cases and environmental swabs were tested for enterovirus nucleic acid by real-time RT-PCR. Eligible positive specimens underwent VP1 amplification, bidirectional Sanger sequencing, typing, and phylogenetic analysis. Attack rates were compared with Pearson chi-square tests, with a fixed-margin Monte Carlo exact test for the class-level comparison.

Results

Sixty-eight outbreak-definition cases were found, all in children. The kindergarten-wide attack rate was 22.08% (68/308), and the child attack rate was 26.15% (68/260). Cases occurred in all 10 classes. Class-specific attack rates varied significantly (chi-square = 25.50, P = 0.002), with the highest rate in Junior Class 1 (52.38%, 11/21). Fever (65 cases, 95.59%), sore throat (40 cases, 58.82%), and pharyngeal redness (38 cases, 55.88%) were the most common manifestations. Among 42 medically attended children, herpangina and acute upper respiratory tract infection were each recorded in 15. Fourteen of 15 case swabs were enterovirus-positive; 13 VP1 amplicons were sequenced and typed as CV-A2. The outbreak sequences shared 99.83%-100.00% nucleotide identity and grouped together phylogenetically.

Conclusions

This multi-class kindergarten outbreak of herpangina was associated with closely related CV-A2 strains. More importantly, the investigation illustrates a practical recognition pathway for a non-notifiable childhood enterovirus illness: dispersed clinical labels were integrated with class- and date-based health-monitoring signals, and VP1 typing provided etiological confirmation. Routine aggregation of health-check, observation, absence, and symptom records can be critical for identifying abnormal clustering before laboratory confirmation is available.

Background

Herpangina is an acute infectious disease of children caused mainly by enteroviruses (EVs). Typical symptoms include fever and sore throat, with vesicular or ulcerative lesions in the oropharynx [1, 2]. Although herpangina and hand, foot, and mouth disease (HFMD) share viral agents and transmission routes, herpangina is not included in China's statutory infectious disease reporting system. Surveillance reports from several Chinese regions show that herpangina occurs predominantly in young children, usually increases in summer or during the summer-autumn season, and may appear as clusters or outbreaks in kindergartens and schools [3, 4]. In a previous Shenzhen kindergarten outbreak, mixed-class activities, contact with ill children, and poor hygiene habits were reported as possible contributors to spread [5]. These findings underscore the role of kindergarten-based routines–illness-related absence follow-up, morning/noon checks, all-day observation, and symptom registration–in detecting unusual increases in illness. Evidence from school- and kindergarten-associated EV outbreaks also supports prompt cluster recognition and timely case and class management [6].

During enterovirus seasons, fever and sore throat do not point to a single diagnosis. Children with early herpangina may be recorded at medical visits as having respiratory tract infection, suspected bacterial infection, fever of unknown cause, or, in some clinical settings, traditional Chinese medicine (TCM) diagnoses. Without a statutory reporting trigger for herpangina, an outbreak can be missed if health-check and absence information is not reviewed continuously by class and onset date. Diagnostic uncertainty between EV infection and suspected bacterial infection has also been described in clinical practice [7, 8]. For kindergartens, therefore, medical-visit labels need to be interpreted together with symptom records and the time-class distribution of illness.

Coxsackievirus A2 (CV-A2) is among the enterovirus serotypes reported in herpangina. Published studies indicate that CV-A2 can cause herpangina epidemics or outbreaks, often involving young children and a high frequency of fever [9–13]. The dominant EV serotypes associated with herpangina differ by place and year, and CV-A2 may not be the serotype most readily suspected in routine clinical surveillance or kindergarten health monitoring. When a cluster involves several classes and the initial diagnoses are heterogeneous, VP1 typing and phylogenetic analysis can help determine whether cases share an etiological link.

In June 2026, a kindergarten in Shenzhen reported a multi-class cluster of fever, sore throat, and oral/oropharyngeal symptoms among children. Early outpatient records included herpangina, acute upper respiratory tract infection, bacterial infection, fever of unknown cause, and a small number of other Western medical or TCM labels. This event provided an opportunity to examine how a non-notifiable enterovirus-associated illness can be recognized through an evidence chain that begins with dispersed clinical labels, becomes visible through class- and date-based clustering of kindergarten health-monitoring data, and is confirmed etiologically by EV nucleic acid testing and VP1 typing. Here, we describe the epidemiological pattern and laboratory evidence for this CV-A2 herpangina outbreak and

discuss how kindergarten health monitoring can be connected with etiological surveillance during enterovirus epidemic seasons.

Methods

Setting and study population

The investigation included all children and staff members in the affected kindergarten. The kindergarten was privately operated and occupied one three-story teaching building with three grades and 10 classes. Junior Classes 1–3 were on the first floor; Middle Classes 1–3 and Senior Class 1 were on the second floor; and Senior Classes 2–4 were on the third floor. At the time of the outbreak, the kindergarten had 260 children (138 boys and 122 girls) and 48 staff members, including one school health worker. After-school interest classes and school bus services were provided.

Case definitions

Operational case definitions were based on the Chinese expert consensus on herpangina diagnosis and treatment and then adapted for field investigation [1]. A suspected case was any child or staff member in the kindergarten who developed fever (> = 37.3 degrees C), sore throat, or oral/oropharyngeal manifestations, including vesicles, rash, or ulcers, between 18 May and 18 June 2026. A clinically diagnosed case was a suspected case diagnosed as herpangina by a medical institution. A laboratory-confirmed case was a suspected or clinically diagnosed case with a throat or anal swab positive for generic enterovirus nucleic acid. For analysis, we included children who met these operational definitions and matched the time, place, and population scope of the outbreak.

Case finding and field investigation

Cases were identified from four sources: on-site review of morning/noon health-check logs, attendance lists, and illness-related absence follow-up records; interviews with the kindergarten director, class teachers, the school health worker, and parents; outpatient logs from nearby medical institutions; and searches of the China Disease Control and Prevention Information System. We used the herpangina line list to record demographic information, clinical manifestations, and medical diagnoses. Field visits and interviews with relevant staff were also used to review disinfection practices in classrooms, toilets, and public activity rooms.

Laboratory testing and sequencing

Combined throat/anal swabs from cases and environmental swabs were collected with reference to the 2009 HFMD prevention and control guideline. Real-time reverse-transcription PCR (real-time RT-PCR) testing was carried out at the Shenzhen Luohu District Center for Disease Control and Prevention. At the

initial stage, specimens were tested for generic enterovirus (EV), CV-A16, and EV-A71 nucleic acid with commercial real-time RT-PCR assays manufactured by Jiangsu BioPerfectus Technologies Co., Ltd. (Jiangsu, China). Generic-EV-positive specimens with sufficient viral load were considered for enterovirus typing and VP1 sequencing. Among 14 generic-EV-positive case specimens, 13 had cycle threshold (Ct) values of 22.45–28.44, met the sequencing laboratory criterion of Ct < 30, and were submitted to Bojie (Qingdao) Medical Technology Co., Ltd. (Qingdao, China) for VP1 amplification and bidirectional Sanger sequencing. The remaining generic-EV-positive specimen had a Ct value of 36.18 and was not sequenced. Before sequencing, PCR products were examined by agarose gel electrophoresis to verify the expected amplicon size. Forward and reverse chromatograms were checked for base-calling quality and assembled; the assembled sequences met the Q20 quality criterion. If unresolved mixed peaks were present, they were represented with International Union of Pure and Applied Chemistry ambiguity codes rather than treated as definitive nucleotide substitutions. This investigation generated partial VP1 amplicon sequences; whole-genome sequencing was not performed.

Bioinformatic and phylogenetic analysis

Assembled VP1 amplicon sequences were reviewed in Sequencher and typed with NCBI BLAST. The 13 outbreak sequences measured 877–889 bp, with an 873-bp region shared by all sequences. Phylogenetic analysis used a 595-bp common homologous region, from which 593 sites remained after complete deletion. The maximum-likelihood tree contained the 13 outbreak sequences, 11 CV-A2 reference sequences covering validated references for genotypes A-D, and CV-A10 strain Kowalik (AY421767) as the outgroup. ModelFinder selected the best-fit nucleotide substitution model. Branch support was estimated with 1,000 ultrafast bootstrap replicates and bootstrap nearest-neighbor interchange optimization. The outbreak genotype was not assigned solely from BLAST results or pairwise similarity.

Statistical analysis

Categorical variables were described as counts, percentages, or attack rates. We compared attack rates by class, floor, grade, and sex using Pearson chi-square tests. A chi-square test for linear trend was applied to the grade-related pattern in attack rates. Because several cells in the class-specific comparison were small, we also ran a fixed-margin Monte Carlo exact test with 1,000,000 simulations. All tests were two-sided, and alpha was set at 0.05. Clinical manifestations, medical diagnoses, laboratory findings, and field investigation observations were summarized descriptively.

Results

Outbreak overview

On 4 June 2026, the Shenzhen Luohu District Center for Disease Control and Prevention was notified that multiple children in a kindergarten had developed fever and sore throat since 28 May. We identified

68 outbreak-definition cases, all among children. The attack rate was 22.08% (68/308) for the whole kindergarten and 26.15% (68/260) among children. No severe illness or death was reported.

The most frequent manifestations were fever (65 cases, 95.59%), sore throat (40 cases, 58.82%), pharyngeal redness (38 cases, 55.88%), oral vesicular lesions (23 cases, 33.82%), and cough (18 cases, 26.47%). Forty-two children (61.76%, 42/68) visited medical institutions. In this group, herpangina and acute upper respiratory tract infection were each recorded in 15 children (35.71% each), followed by fever of unknown cause in 5 children (11.90%), bacterial infection in 4 children (9.52%), viral infection in 1 child (2.38%), and two TCM labels–shanghuo (internal heat) and houbi (throat impediment)--in 1 child each (2.38% each). The TCM labels were kept as they appeared in outpatient records and were not reclassified as Western medical diagnoses. The other 26 children (38.24%, 26/68) did not seek medical care and were isolated for observation at home.

The first case was a child from Middle Class 2 with low-grade fever on 28 May. Case numbers rose during the three-day holiday from 30 May to 1 June and reached a peak of 26 cases on 2 June. Another 13 cases occurred on 3 June, after which only sporadic onsets were recorded (Fig. 1).

Spatial and demographic distribution

All 10 classes had cases. Attack rates showed statistically significant differences by floor (chi-square = 9.74, P = 0.008) and by class (chi-square = 25.50, P = 0.002). The first floor had the highest rate (37.50%, 21/56), followed by the second floor (29.20%, 33/113) and the third floor (15.38%, 14/91). At the class level, Junior Class 1 ranked highest (52.38%, 11/21), followed by Junior Class 2 (45.00%, 9/20). The class-level result was unchanged in the Monte Carlo exact sensitivity analysis (P = 0.00217) (Table 1).

Table 1

Attack rates by floor and class in the herpangina outbreak in a kindergarten in Shenzhen Note: Attack rates were calculated using the corresponding subgroup denominator. Pearson chi-square tests were used for group comparisons. For the class-level comparison, a Monte Carlo exact test with fixed margins was additionally performed because some cell counts were small.

Characteristic	Group	Cases	Population	Attack rate (%)	χ^2 / P value
Floor	First floor	21	56	37.50	χ^2=9.74, P = 0.008
	Second floor	33	113	29.20	
	Third floor	14	91	15.38	
Class	Junior 1	11	21	52.38	χ^2=25.50, P = 0.002
	Junior 2	9	20	45.00	
	Middle 1	10	27	37.04	
	Middle 3	8	28	28.57	
	Senior 1	8	30	26.67	
	Senior 4	8	31	25.81	
	Middle 2	7	28	25.00	
	Senior 3	5	29	17.24	
	Junior 3	1	15	6.67	
	Senior 2	1	31	3.23	

All cases occurred in children; no illness was reported among staff members. The attack rate was similar in boys (26.81%, 37/138) and girls (25.41%, 31/122), with no statistically significant sex difference (chi-square = 0.07, P = 0.797). Cases were 3–6 years of age, with a median of 4 years. Attack rates differed among grade groups (chi-square = 8.39, P = 0.015) and declined as grade level increased (trend chi-square = 8.25, P = 0.004) (Table 2).

Table 2
Attack rates by grade group and sex in the herpangina outbreak in a kindergarten in Shenzhen Note: Attack rates were calculated using the corresponding subgroup denominator. Pearson chi-square tests were used for group comparisons, and a chi-square test for linear trend was used for grade group analysis.

Characteristic	Group	Cases	Population	Attack rate (%)	χ^2 / P value
Grade group	Junior	21	56	37.50	χ^2=8.39, P = 0.015
	Middle	25	83	30.12	
	Senior	22	121	18.18	
Sex	Male	37	138	26.81	χ^2=0.07, P = 0.797
	Female	31	122	25.41	

Laboratory and molecular findings

Fifteen combined throat/anal swabs from cases and five environmental samples were obtained. Fourteen case swabs were positive for generic EV nucleic acid, corresponding to a positivity rate of 93.33%. One of the 14 positive specimens was not sent for sequencing because its Ct value was > 30. The other 13 specimens yielded assembled VP1 amplicon sequences, and all were identified as CV-A2. The five environmental samples, collected from toilet taps, buttons, desks, toys, and related surfaces, were negative.

The 13 assembled CV-A2 VP1 amplicon sequences were 877–889 bp long. They shared a 873-bp coverage region and showed 99.83%-100.00% nucleotide identity with one another. Similarity to the CV-A2 prototype strain was 82.18%-82.35%. In the phylogenetic analysis, which used a 595-bp common homologous region and retained 593 sites after complete deletion, the 13 outbreak sequences formed a single cluster. This clustering supported a close etiological link among the sequenced cases (Fig. 2).

Field investigation findings

Field investigation showed several opportunities for contact between classes or through shared spaces. Junior Classes 1 and 2, Senior Class 1 and Middle Class 1, Middle Classes 2 and 3, and Senior Classes 3 and 4 shared toilets. Disinfection records for toilets and classrooms were incomplete, and some classrooms had ventilation from only one side. On 28 May, the kindergarten held an outdoor Children's Day water-play activity. Although the activity was arranged by class and in batches, the activity zones had no physical barriers, and water-play items were shared.

Discussion

Outbreak characteristics and early recognition

The main contribution of this investigation is not only the identification of CV-A2, but also the demonstration of a practical evidence chain for recognizing a non-notifiable herpangina outbreak in a kindergarten. The outbreak affected 68 children in all 10 classes, with an attack rate of 26.15% among children. The highest rates were concentrated in Junior Classes 1 and 2, a pattern more consistent with a recognized outbreak than with unrelated sporadic illnesses. Fever, sore throat, and pharyngeal redness dominated the clinical presentation, and no severe cases or deaths occurred. The timing from late May to mid-June was also compatible with the summer or summer-autumn peak of herpangina reported in several Chinese regions [3, 4].

The main challenge at the beginning of the event was not the absence of illness, but the scattered way in which illness was labeled. Among 42 children who attended medical institutions, 15 were recorded as herpangina and another 15 as acute upper respiratory tract infection; the remaining diagnoses included fever of unknown cause, bacterial infection, viral infection, shanghuo, and houbi. Early EV infection can present as fever and sore throat before typical oral findings are recognized, and differentiation from suspected bacterial infection may be difficult [7, 8]. If a kindergarten relies only on individual outpatient diagnoses, related cases occurring in the same short time window may not be connected promptly.

For this reason, the class-by-date pattern was central to verification. Cases accumulated over a short interval, and Junior Classes 1 and 2 had attack rates of 52.38% and 45.00%, respectively. Before recognition of the outbreak, a Children's Day water-play activity had been held by class and in batches, but the areas were not separated by physical barriers and water-play items were shared. In addition, some classrooms had limited ventilation, and toilet and classroom disinfection records were incomplete. A previous Shenzhen kindergarten investigation of herpangina reported that mixed-class group activities and contact with cases could create transmission opportunities, while hot weather and air-conditioner use might reduce indoor ventilation [5]. These observations help explain the multi-class distribution in the present event, but they should not be read as independent risk factors because no case-control or cohort study was conducted.

Etiological evidence and interpretation

The laboratory findings strengthened the epidemiological interpretation. Fourteen of the 15 case swabs were positive for generic EV nucleic acid. All 13 VP1 amplicons that were successfully sequenced were typed as CV-A2, and these sequenced cases came from six classes. The sequences showed 99.83%-100.00% nucleotide identity and formed a single phylogenetic cluster. When considered together with the shared time, place, and population at risk, the molecular results support a genetically related CV-A2 outbreak.

CV-A2 has circulated continuously in China and has shown genetic diversity; it has also been reported in herpangina outbreaks involving kindergartens or child populations [14–16]. In the present outbreak, VP1 sequencing was useful because clinical labels alone did not clearly connect all cases. Nevertheless, the VP1 region has a limited interpretive scope. These data cannot establish the original infection source, the direction of spread, or individual transmission chains.

Implications for linking kindergarten health monitoring with etiological surveillance

Herpangina is not a statutory notifiable infectious disease in China. Medical-institution-based sentinel surveillance and laboratory-based etiological surveillance are valuable for describing pathogen spectra and serotype changes among children who seek care. In kindergartens, however, the earliest warning usually comes from routine health work inside the school rather than from a single medical diagnosis. The present investigation shows how such information can be organized into an evidence chain: outpatient labels indicated illness but were heterogeneous; class- and date-based aggregation showed abnormal clustering; and EV testing plus VP1 typing confirmed the etiological link. In this outbreak, early labels included herpangina, acute upper respiratory tract infection, fever of unknown cause, bacterial infection, viral infection, and two TCM labels. Morning/noon health checks, all-day observation, illness-related absence follow-up, and symptom registration therefore need to be reviewed by class and by date, especially for fever, sore throat, pharyngeal redness, and oral vesicular lesions.

Cluster verification should begin when several children in the same class develop fever, sore throat, or oral/oropharyngeal symptoms within a short interval, or when similar symptoms rise across several classes at the same time, even if early outpatient or TCM labels are inconsistent. After the response begins, sampling should cover different onset dates, classes, symptom patterns, and diagnostic-label categories where possible. Timely etiological feedback from the district CDC, together with strengthened hospital-based surveillance, may help clinicians interpret atypical presentations and non-herpangina labels such as suspected bacterial infection or TCM diagnoses. EV nucleic acid testing and VP1 typing are therefore best viewed as complements to clinical assessment, medical-institution surveillance, and field epidemiology, not as replacements for daily kindergarten health monitoring.

Limitations

Several limitations should be considered. First, case finding depended on health-monitoring records, illness-related absence follow-up, and field investigation data; some oral or oropharyngeal signs may not have been completely documented. Second, not every registered case was sampled. Third, the investigation did not use a case-control or cohort design, so the independent contribution of water-play activities, shared toilets, ventilation, disinfection, or other behavioral and environmental factors could not be estimated. Fourth, only a small number of environmental samples were collected, and negative results cannot rule out contamination or contact transmission before sampling. Finally, the molecular evidence was limited to generic EV detection and assembled partial VP1 amplicon sequences. Whole-genome sequencing and recombination analysis were not performed, and genotype assignment and broader evolutionary inference for the outbreak cluster were therefore limited. Viral whole-genome characteristics, possible recombination events, infection source, and direction of person-to-person spread could not be determined.

Conclusions

This investigation confirmed a multi-class kindergarten herpangina outbreak caused by CV-A2 and clarified a practical evidence chain for recognizing a non-notifiable enterovirus-associated illness: dispersed clinical labels first suggested a broader illness pattern, class-date aggregation of kindergarten health-monitoring data revealed abnormal clustering, and VP1 typing provided etiological confirmation. During outbreak response, real-time RT-PCR, VP1 typing, and prompt etiological feedback to clinicians can help interpret dispersed or atypical clinical presentations and can connect kindergarten health monitoring, hospital-based etiological surveillance, and field epidemiology.

Abbreviations

Ct
cycle threshold
CV-A2
coxsackievirus A2
CV-A10
coxsackievirus A10
EV
enterovirus
HFMD
hand, foot, and mouth disease
RT-PCR
reverse-transcription PCR
TCM
traditional Chinese medicine
VP1
viral protein 1.

Declarations

Ethics approval and consent to participate

The study was reviewed and approved by the Ethics Review Committee of Shenzhen Luohu District Center for Disease Control and Prevention. The analysis used de-identified information collected during a public health outbreak investigation and routine response. No personally identifying information is disclosed in this manuscript. The approval number will be added if available.

Consent for publication

Not applicable.

Availability of data and materials

The case-level dataset contains potentially identifiable public health surveillance information and is not publicly available. De-identified aggregate data may be provided by the corresponding author on reasonable request and after institutional approval. The VP1 sequences generated in this study have been submitted to GenBank and assigned accession numbers PZ791044-PZ791056 (LH1-LH13).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Yanmei Wang contributed to field investigation, data collation, formal analysis, and writing of the original draft. Yizhou Deng and Qiumei Li performed real-time RT-PCR testing and coordinated sequence testing. Sijie Zheng, Saicai Mao, and Lulu Huang contributed to field investigation and specimen collection. All authors reviewed and approved the final manuscript.

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Figures

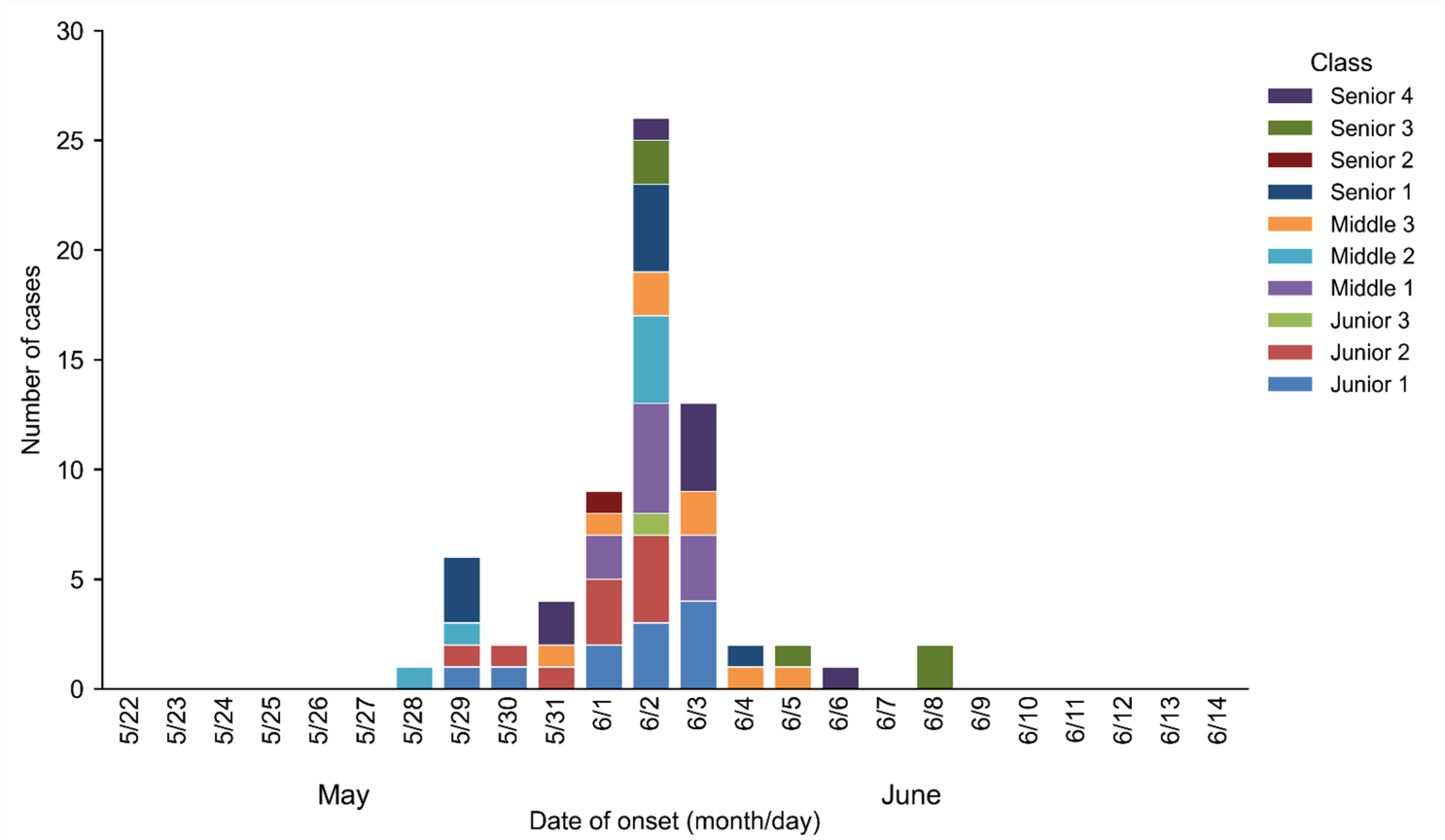


Figure 1

Distribution of herpangina cases by date of onset and class during the case-search period. Bars are stacked by class and were generated from the 68 outbreak-definition cases. Dates with no cases are retained to show the case-search window and outbreak time course.

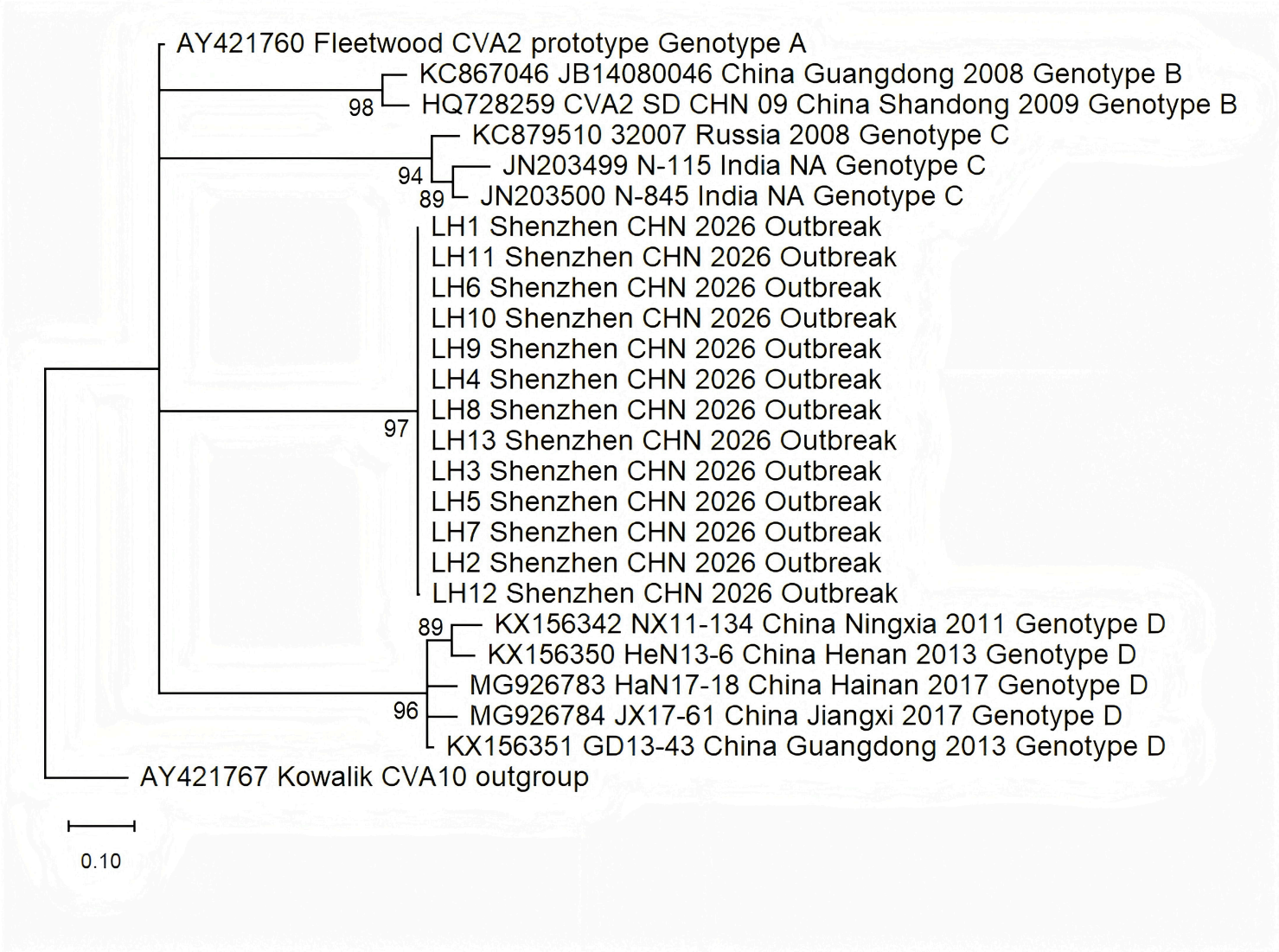


Figure 2

Maximum-likelihood phylogeny of CV-A2 based on a common VP1 region. The analysis included 13 outbreak sequences, 11 CV-A2 reference sequences, and CV-A10 strain Kowalik (AY421767) as the outgroup. Of the 595-bp common region, 593 sites were retained after complete deletion. Ultrafast bootstrap values ≥70% are shown. The 13 outbreak sequences clustered together, supporting a genetically related CV-A2 outbreak. Genotype assignment of the outbreak cluster was not inferred from this partial-VP1 analysis

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