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Short report

Non-mumps parotitis associated with influenza A/H3N2: A case series from Southern Italy during the 2024–2025 influenza season

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ABSTRACT

Parotitis, commonly associated with the mumps virus, can also result from other viral infections. We report a case series of 21 children and preadolescents presenting with mumps-like parotitis in Southern Italy between January and February 2025, all of whom had been vaccinated against mumps. In all cases, mumps virus was not detected by real-time PCR in clinical samples. Alternative etiologies were investigated by testing for a broad panel of pathogens. Viral infections were identified in 16 cases (76.2 %), with influenza A/H3N2 being the most common pathogen (14 cases, 87.5 %), followed by rhinovirus and coronavirus NL63. Of the 14 patients positive for influenza A/H3N2, 10 had received influenza vaccine. Whole genome sequencing of A/H3N2 viruses from three samples was performed, and phylogenetic analysis of the hemagglutinin (HA) gene revealed that they belonged to the A/H3N2 subclade 2a.3a.1 (J.2), clustering with other regional viruses from the 2024– 2025 season. No unexpected genetic variations were found in target genes that would suggest changes in tissue tropism. Given the emergence of influenza A/H3N2 as a potential etiological agent of non-mumps parotitis, particularly during epidemic periods, enhanced surveillance and comprehensive diagnostic approaches are needed to improve understanding of the epidemiology of non-mumps parotitis.

Introduction

Mumps is characterized primarily by unilateral or bilateral inflammation of the parotid glands, manifesting as painful swelling and it most frequently affects school-aged children and adolescents [1,2]. Potential complications include orchitis, pancreatitis, glomerulonephritis, encephalitis, and sensorineural hearing loss [1].

Non-mumps parotitis, though less prevalent, has been associated with several viral etiologies, including Epstein-Barr virus (EBV), influenza A and B viruses, adenoviruses, enteroviruses, and human herpesviruses (HHV) [3–10]. A series of parotitis cases in children linked to influenza A/H3N2 infection were reported in England and USA during the 2014–2015 winter season [3,6,11].

In 2023, only one case of mumps was reported and confirmed in the Apulia region.

During the year-round surveillance period in 2024, a total of 24 suspected cases were reported, with mumps virus infection confirmed in 13 cases (54.2 %). In 2025, an unexpected cluster of 21 suspected mumps cases was reported within a single month, yet none were confirmed as mumps virus infections. In light of the increase in the number of reported cases of non-mumps parotitis, the regional mumps laboratory conducted investigations to identify alternative etiologies.

In this case series, we report multiple cases of non-mumps parotitis associated with influenza A/H3N2 infection, occurring in children and preadolescents during the peak of the 2024–2025 influenza season. Clinical presentations and virological characteristics of the virus were investigated.

Case series

Between 22nd January and 21st February 2025, a total of 21 suspected cases of mumps were referred to the Laboratory of Molecular Epidemiology and Public Health of the Hygiene Unit -

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A.O.U.C. Policlinic of Bari for diagnostic assessment of mumps. Most patients were males (76 %) and all patients were aged < 16 years (median age: 9 years; interquartile range, IQR: 6–11 years). All cases presented with unilateral or bilateral painful parotid swelling, fever and lymph node enlargement in the homolateral submandibular, retroauricular or laterocervical regions. In all cases, parotid swelling was preceded by fever occurring 1–10 days earlier and lasted 1–3 days without further complications.

All patients were vaccinated with the live attenuated vaccine against mumps. None of the patients had pre-existing chronic conditions.

Nasopharyngeal, buccal and oropharyngeal swabs were collected in the presence of parotid swelling. At the time of swab collection, the patients reported respiratory symptoms and fever for a period ranging from 1 to 21 days prior (median 4 days, IQR 3–7). All samples were tested for mumps virus by real-time PCR (VIASURE Mumps, Enterovirus & Parechovirus Real-Time PCR, Clonit, Milan, Italy). All samples resulted negative for the mumps virus. A serum sample was collected for 8 patients, and all were positive for anti-mumps IgG and negative for anti-mumps IgM (MUMPS VIRCLIA® IgG, IgM MONOTEST, Vircell, Granada, Spain).

The samples were then tested for EBV, Cytomegalovirus (CMV), parvovirus B19, HHV6, and HHV7 using a commercial real-time PCR (Allplex™ Meningitis-V1 Assay, Seegene, Seoul, South Korea). All samples were negative for these pathogens.

Successively, the samples were tested for influenza viruses A and B, parainfluenza viruses, respiratory syncytial virus, metapneumovirus, rhinovirus, enterovirus, bocavirus, human coronaviruses (OC43, NL63, 229E), adenovirus, *Bordetella parapertussis, Bordetella pertussis, Chlamydophila pneumoniae, Haemophilus influenzae (HI), Legionella pneumophila, Mycoplasma pneumoniae, Streptococcus pneumoniae* by real-time PCR (Allplex™ Respiratory panel 1–2–3, and Allplex™ PneumoBacter Assay, Seegene, Seoul, South Korea). Samples were also tested for SARS-CoV-2 (TaqPath COVID-19 Diagnostic PCR Kit, Thermo Fisher Scientific, Waltham, MA, USA). Influenza A/H3N2 was identified in 14 samples (66.7 % of cases). Co-infections with A/H3N2 were observed in two cases with rhinovirus and coronavirus NL63, respectively. Two patients were positive for rhinovirus. Five patients were negative for all respiratory viruses and bacteria tested. Their median age was 10.2 years (IQR: 10–11), and the onset of respiratory symptoms occurred, on average, 8 days earlier (range: 2–21 days).

Demographic characteristics, influenza vaccination status and molecular test results are summarized in Table 1.

Data on influenza vaccination status was retrieved for all patients from the regional GIAVA vaccination registry (https://giava.sanita.puglia.it/).

Whole Genome Sequencing (WGS) was performed on the three samples with a Cycle Threshold < 30 in real-time PCR, using the MiSeq platform (Illumina Inc., San Diego, CA, USA).

The phylogenetic tree of the HA gene and HA substitution analysis were constructed by the neighbor joining method using MEGAX software. All strains belonged to subclade 3 C.2a1b (J.2) (Fig. 1). No unexpected genetic variations were found in target genes.

Discussion

We report 21 cases of mumps notified in the province of Bari (Apulia region), an area with very low mumps incidence, occurring between January and February 2025.

Sixty-seven percent (14/21) of the samples tested positive for influenza A/H3N2 virus, suggesting an association with clinical manifestations of parotitis.

In Italy, this is the first report of non-mumps parotitis associated with influenza A/H3N2, with the exception of a single case of Coronavirus-A/H3N2 influenza virus co-infection in Sicily in 2023 [9].

Our findings are consistent with previously reported cases of parotitis associated with influenza A/H3N2 virus in United States, Canada and England [3,4,6].

The 2024– 2025 influenza season in Apulia was marked by heightened activity, with influenza-like illness incidence peaking in weeks 3 and 4 of 2025 (late January), reaching rates of 19.8 and 20.1 cases per 1000 inhabitants, respectively (https://respivirnet.iss.it/pagine/rapportoInflunet.aspx).

Despite the co-circulation of multiple influenza subtypes in Apulia during the seasonal peak, only influenza A/H3N2 was detected in the parotitis cases analyzed in our cohort. This finding is consistent with prior reports of epidemiological links between A/H3N2 and parotid swelling [3–6,9]. However, the pathophysiological mechanisms underlying this association remain unclear [12].

Table 1
Characteristics demographics, vaccination status and real-time PCR results of children with parotid gland swelling, tested negative for mumps virus, Apulia January-February 2025.

Patients characteristics			Flu vaccination status	Real-time PCR results		
Sex	Age (years)	Comorbidity		Influenza viruses	Other respiratory viruses	SARS-CoV-2
M	5	No	inactivated	**influenza A/H3N2**	**coronavirus NL63**	Negative
M	6	No	inactivated	**influenza A/H3N2**	Negative	Negative
M	7	No	inactivated	**influenza A/H3N2**	Negative	Negative
M	10	No	inactivated	Negative	**rhinovirus**	Negative
M	10	No	inactivated	Negative	Negative	Negative
F	11	No	inactivated	**influenza A/H3N2**	Negative	Negative
M	6	No	live attenuated	**influenza A/H3N2**	Negative	Negative
M	7	No	live attenuated	**influenza A/H3N2**	Negative	Negative
M	9	No	live attenuated	**influenza A/H3N2**	**rhinovirus**	Negative
M	9	No	live attenuated	**influenza A/H3N2**	Negative	Negative
F	1	No	not vaccinated	**influenza A/H3N2**	Negative	Negative
M	3	No	not vaccinated	**influenza A/H3N2**	Negative	Negative
F	5	No	not vaccinated	**influenza A/H3N2**	Negative	Negative
F	8	No	not vaccinated	Negative	Negative	Negative
M	9	No	not vaccinated	Negative	**rhinovirus**	Negative
M	10	No	not vaccinated	Negative	Negative	Negative
M	11	No	not vaccinated	**influenza A/H3N2**	Negative	Negative
F	11	No	not vaccinated	Negative	Negative	Negative
M	12	No	not vaccinated	Negative	Negative	Negative
M	12	No	not vaccinated	**influenza A/H3N2**	Negative	Negative
M	12	No	not vaccinated	**influenza A/H3N2**	Negative	Negative

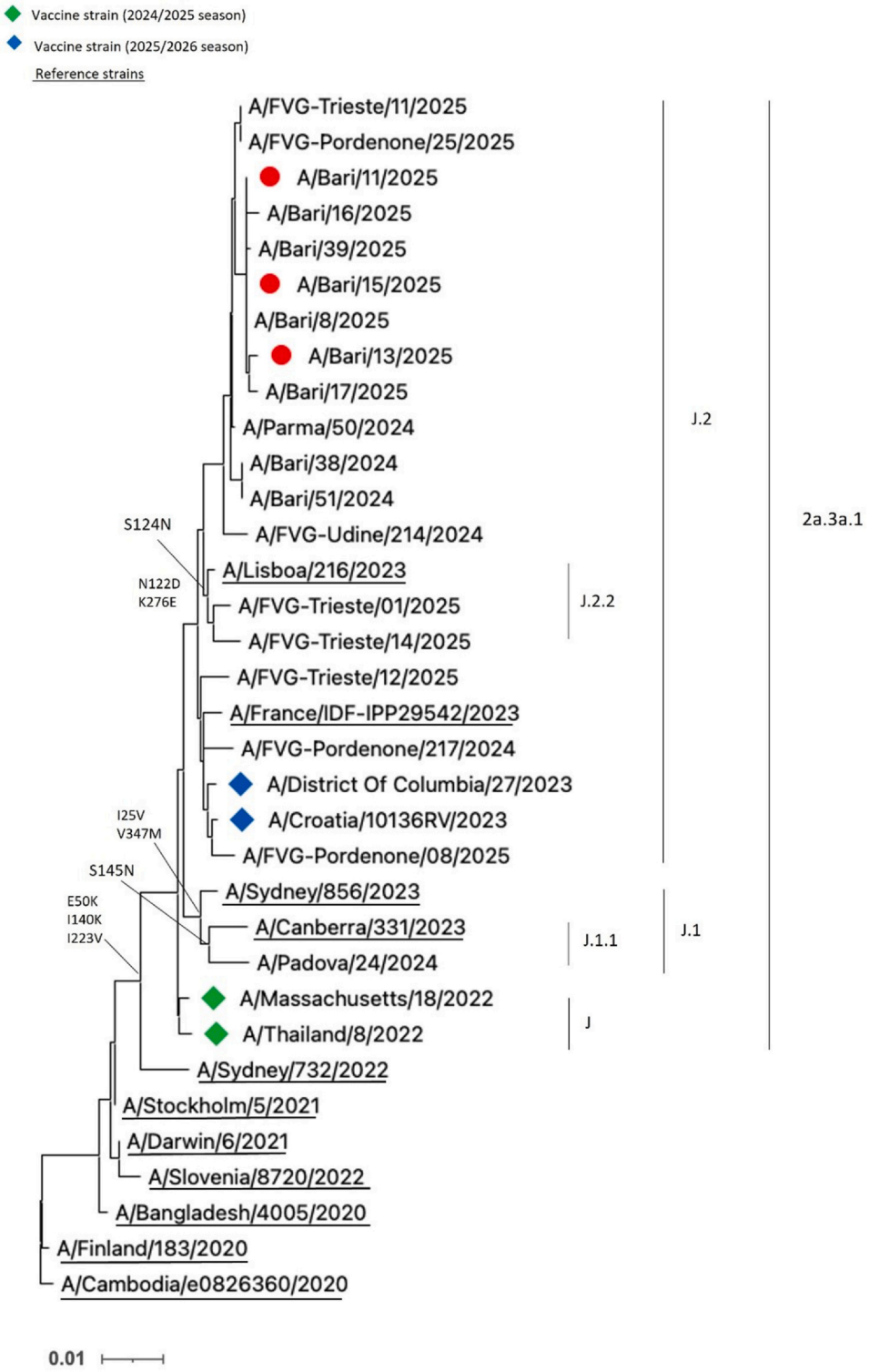

Fig. 1. Phylogenetic analysis of the HA gene sequences of influenza A/H3N2 virus from pharyngeal swab samples of children with suspected mumps, Apulia, January-February 2025. Sequences obtained from our study are marked with red dots. Accession number: EPI_ISL_19725208 for the strain A/Bari/13/2025, EPI_ISL_19725270 for the strain A/Bari/15/2025 and EPI_ISL_19725202 for the strain A/Bari/11/2025. All others are GenBank reference sequences.

Phylogenetic analysis of the HA gene from the three sequenced strains revealed high similarity among them, with no genetic divergence from other A/H3N2 strains circulating in the pediatric population of Bari Province during the 2024/2025 season. Furthermore, these strains harbored the amino acid substitutions I140K and I223V, which are also present in the A/H3N2 vaccine reference strains for the 2024–2025 season (*A/Thailand/8/2022* and *A/Massachusetts/18/2022*).

Two children negative for influenza tested positive for rhinovirus. To our knowledge, no prior cases of rhinovirus-associated parotitis have been reported in the literature.

Five cases tested negative for all targeted pathogens. Delayed sampling may account for the failure to identify a causative agent, as

optimal pathogen detection requires collection during peak viral shedding. Alternatively, given the clinical presentation focused on parotitis, we hypothesize that enlargement and inflammation of the parotid gland may represent a late complication of viral respiratory infections, such as influenza. Parotitis typically manifests after initial respiratory symptoms, potentially coinciding with waning viral loads below detection thresholds. This hypothesis aligns with the observed temporal dissociation between acute respiratory infection phases and parotitis onset.

Notably, our pediatric cohort lacked underlying comorbidities. Further investigation is needed to identify potential host or pathogen-specific factors that predispose individuals to non-mumps viral parotitis.

Although influenza A/H3N2 virus mainly causes acute respiratory infection, parotitis may be a rare complication. In our study, 8/14 children were vaccinated against influenza, therefore it can be conceived that influenza vaccination might not be able to prevent the occurrence of this specific complication. Although less common than mumps-associated parotitis, influenza-related parotitis can mimic its clinical features and complications, underscoring the need for differential diagnosis, targeted management (e.g., antiviral therapy), and public health surveillance. Further studies should investigate the epidemiology, pathogenesis, and immune-mediated mechanisms of non-mumps viral parotitis, particularly in influenza-endemic settings.

Ethics approval and consent to participate

All activities conducted during the course of the study were part of the legislated mandate of the Health Promotion and Public Health Department of the Apulia region (Italy); therefore, approval by the Ethics Committee was waived. All procedures were performed in accordance with the Declaration of Helsinki, as revised in 2013, for research involving human subjects. Written informed consent was obtained from the children's parents.

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CRediT authorship contribution statement

MC, LP and FC conceived the idea for the study. LP, AM and VAO obtained the data. FC, RM cleared up the datasets; FC, AS, DC and RM performed the data analyses. AS, FC, RM interpreted the results of the data analyses. FC, RM and MC wrote the manuscript. All authors read and approved the final manuscript.

Data availability

The data used and/or analyzed for this short report are available from the corresponding author.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Chironna maria reports financial support was provided by European Union. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Consent for publication

Not applicable.

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