

Reye syndrome or not: an age-old enigma about influenza encephalopathy deaths in children

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This article was published on 28 Nov 2025 at www.hkmj.org.

Hong Kong Med J 2025;31:Epub

<https://doi.org/10.12809/hkmj2411800>

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Paediatric perspectives on occasional influenza morbidity and rare mortality in Hong Kong in the pre-COVID-19 era have been discussed.^{1,2} The world is now facing a rebound of viral respiratory infections, with an increase in paediatric intensive care admissions in the post-COVID-19 era.³ Sadly, in 2024, the Centre for Health Protection reported two cases of influenza-related mortality. A fully influenza-vaccinated child developed fulminant encephalopathy and hepatopathy (with elevated intracranial pressure and cerebral herniation, coagulopathy, deranged liver function without jaundice, hyperammonaemia, or hypoglycaemia) and died within 2 days.⁴ There was no history of aspirin consumption, but the child had received herbal medicine prior to the development of encephalopathy. Earlier, another unvaccinated toddler died shortly after developing acute encephalopathy and cerebral oedema associated with influenza.⁵

Influenza has received global attention, except perhaps during the peak COVID-19 era from 2020 to 2022. It is a respiratory virus for which both prophylaxis through immunisation and treatment with specific antiviral medications are readily available.⁶ Severe influenza complications, particularly encephalopathy, occur every year, especially in unvaccinated children who do not receive antiviral treatment.¹ In 2020, during the early period of the COVID-19 pandemic, we successfully managed a child with high fever, seizures, and an altered conscious state.² Nasopharyngeal aspirate testing confirmed influenza A H1-2009. The child was treated with the antiviral oseltamivir. Cerebral oedema was promptly relieved with dexamethasone, hypertonic saline, and mannitol infusion. The child stabilised after 48 hours of paediatric intensive care. Neither the mother nor the child had received the seasonal influenza vaccination. This case demonstrates that, despite potential serious sequelae, influenza-associated encephalopathy can be successfully treated with prompt critical care

management.^{2,7}

Pre-pandemic live-attenuated influenza vaccination might potentially reduce childhood mortality in Hong Kong.⁸ A recent study by Chiu et al⁹ estimated that the effectiveness of influenza vaccination in reducing hospitalisation among children was 90%. Fortunately, despite the high influenza burden among Hong Kong children, mortality and severe complications remain generally low.^{1,10} Nevertheless, severe influenza complications in children have occurred annually, primarily among the unvaccinated, and have accounted for one to three deaths each year in Hong Kong.¹ Recently, two cases of acute necrotising encephalopathy in unvaccinated paediatric patients were reported in the Hong Kong medical literature.¹¹ A publication in the *Hong Kong Medical Journal* reported that *SFTPB* and *PDE3A* are independent host susceptibility genes for severe influenza A (H1N1) infection in the Hong Kong Chinese population.¹²

We now have sufficient data in the Hong Kong literature to reassure the public that influenza vaccination is recommended as prophylaxis to reduce the already low complication rates among children. Increased vaccination coverage will also enhance herd immunity against influenza viruses. Other measures to reduce the incidence of seasonal influenza in the community include regular handwashing, avoiding contact with individuals who have respiratory illnesses, practising respiratory hygiene and cough etiquette, and wearing masks during epidemics. With heightened attention to personal hygiene and widespread mask-wearing, the incidence of influenza and respiratory viral diseases was greatly reduced in 2003 during the outbreak of the severe acute respiratory syndrome. These measures were also instrumental in combating the COVID-19 outbreak in 2019.¹³

Two perplexing dilemmas arise from the recent fatal cases. First, could children develop fulminant fatal encephalopathy despite receiving effective

immunisations and antiviral treatment? This concern is often raised by anti-vaccine proponents. Although neurological complications after influenza vaccination have been reported, fatal encephalopathy following influenza infection in vaccinated children had not been reported until recently.^{14,15} Thus, the recent case of fatal acute encephalopathy in a vaccinated child⁴ is exceptionally unusual.

Second, could fatal encephalopathy with hepatopathy result from Reye syndrome?^{14,15} Reye syndrome associated with influenza infection was not uncommon before 1980, but its prevalence substantially dropped after warnings against aspirin use in children during viral infections were issued in the mid-1980s.¹⁶ In a recent report from the United States, the incidence of Reye syndrome was only two among approximately 30 000 influenza-associated hospitalisations (0.01%), whereas encephalopathy occurred in 1.7%.¹⁷ It is a rapidly progressive brain disease.^{14,15} Symptoms of Reye syndrome include vomiting, personality changes, confusion, seizures, and loss of consciousness. Whereas liver toxicity and hepatomegaly typically occur in the syndrome, jaundice usually does not.^{14,15} Death occurs in 20% to 40% of those affected, and about one-third of survivors experience clinically significant brain damage.^{14,15,18} Treatment includes rigorous intracranial pressure control, as well as the use of dexamethasone, mannitol, intravenous immunoglobulin, and tocilizumab.¹⁹ The exact cause of Reye syndrome remains unknown.^{14,15} The syndrome usually begins shortly after recovery from a viral infection, especially influenza or chickenpox. About 90% of reported paediatric cases are associated with aspirin (salicylate) use.^{14,15} Accordingly, aspirin should be avoided in children, except in those with Kawasaki disease.¹⁸ Importantly, many herbal and proprietary medicines contain undisclosed salicylate, aspirin, or aspirin-like compounds.^{20,21} The possibility that herbal medicine contributed to Reye syndrome cannot be excluded, although other potential triggers include non-steroidal anti-inflammatory drugs, influenza, chickenpox, and inborn errors of metabolism.^{15,18,22} The diagnosis of Reye syndrome greatly decreased in the 1980s, when genetic testing for inborn errors of metabolism became available in industrialised nations.²³ A study of 49 Reye syndrome cases showed that most surviving patients had underlying metabolic disorders, including fatty acid oxidation defects such as medium-chain acyl-CoA dehydrogenase deficiency.²⁴

Laboratory abnormalities observed in patients with Reye syndrome include considerably elevated aminotransferase activity, hyperammonaemia, hypoglycaemia, prolonged prothrombin time, and metabolic acidosis.^{14,15} However, Reye syndrome remains a clinical diagnosis; affected

patients typically present with hepatopathy and encephalopathy. The syndrome most commonly affects children,^{14,15} and most cases occur in winter or spring. Reye syndrome affects fewer than one in a million children worldwide each year.^{14,15} Other risk factors include inborn errors of metabolism¹⁸ and genetic aberrations such as RANBP2.

The US Centers for Disease Control and Prevention has defined Reye syndrome using the following criteria: (1) clinically documented acute non-inflammatory encephalopathy with altered consciousness; and (2) cerebrospinal fluid containing ≤ 8 leukocytes/mm³, or cerebral oedema without perivascular or meningeal inflammation in histological specimens.²⁵ Hepatopathy should be documented by liver biopsy, autopsy consistent with Reye syndrome, or a ≥ 3 -fold increase in serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, or serum ammonia levels. There should be no other reasonable explanation for the cerebral and hepatic abnormalities. In practice, not all investigations, such as lumbar puncture or liver biopsy, can be performed in a critically ill child. Consequently, the diagnosis is often made by exclusion and remains largely clinical. In this particular case, influenza complicated by Reye or Reye-like syndrome with hepatopathy and encephalopathy leading to the child's death remains a possibility that cannot be excluded.^{14,15,26–28} Thus, the diagnosis of Reye syndrome is primarily clinical; histological confirmation is rarely performed or required. The diagnosis of Reye syndrome in a patient with neurological manifestations can be challenging. The differential diagnosis includes conditions that cause vomiting and altered consciousness, or so-called Reye-like syndromes, such as inborn errors of metabolism, neuromuscular diseases, meningitis, encephalitis, adverse drug reactions, and toxic exposures to plants and chemicals that induce encephalopathy and hepatocellular injury.¹⁵ The management is supportive. Hong Kong has invested substantial efforts in preventing and managing common and emerging respiratory infections. Meanwhile, the Centre for Health Protection reports new influenza mortality and morbidity in unvaccinated children as the winter surge approaches in 2025.^{29,30} Rather than arousing fear through rare, isolated tragic cases, authorities should take the opportunity to reassure the public that influenza-associated mortality is rare and morbidity remains occasional. The promotion of good health practices—such as immunisations, avoidance of aspirin-containing compounds, prompt diagnosis, and rapid initiation of treatment for children with influenza—cannot be over-emphasised. Efforts to reduce vaccine phobia and hesitancy remain integral components of effective preventive medicine.²⁰

Author contributions

All authors contributed equally to the concept or design, acquisition of data, analysis or interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As an editor of the journal, KL Hon was not involved in the peer review process. Other authors declared no conflicts of interest.

Funding/support

This commentary received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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