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Acute disseminated encephalomyelitis and transverse myelitis following COVID-19 vaccination – A self-controlled case series analysis

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Highlights

- We have identified an association between ChAdOx1 nCoV-19 and an increased risk of Acute Disseminated Encephalomyelitis incident admissions.
- Dose-specific analysis suggests that dose 1 of ChAdOx1 nCoV-19 may be associated with an increased risk of both Acute Disseminated Encephalomyelitis and Transverse Myelitis incident admissions.
- These findings build upon the recently published Global Vaccine Data Network study that suggested an excess of Acute Disseminated Encephalomyelitis and Transverse Myelitis following adenoviral vectored ChAdOx1 nCoV-19 (AZD1222) and mRNA-1273 vaccines compared to historically expected background rates.
- This study demonstrates the value of the Global Vaccine Data Network collaboration leveraging large population sizes to examine important vaccine safety questions regarding rare potential associations, as well as the value of linked population level datasets such as VSHL able to rapidly explore associations that are identified.

Abstract

Acute Disseminated Encephalomyelitis (ADEM) and Transverse Myelitis (TM) are within the group of immune mediated disorders of acquired demyelinating syndromes. Both have been described in temporal association following various vaccinations in case reports and case series and have been evaluated in observational studies. A recent analysis conducted by The Global Vaccine Data Network (GVDN) observed an excess of ADEM and TM cases following the adenoviral vectored ChAdOx1 nCoV-19 (AZD1222) and mRNA-1273 vaccines, compared with historically expected background rates from prior to the pandemic. Further epidemiologic studies were recommended to explore these potential associations.

We utilized an Australian vaccine datalink, Vaccine Safety Health-Link (VSHL), to perform a self-controlled case series analysis for this purpose. VSHL was selected for this analysis as while VSHL data are utilised for GVDN association studies, they were not included in the GVDN observed expected analyses. The VSHL dataset contains vaccination records sourced from the Australian Immunisation Register, and hospital admission records from the Victorian Admitted Episodes Dataset for 6.7 million people. These datasets were used to determine the relative incidence (RI) of G040 (ADEM) and G373 (TM) ICD-10-AM coded admissions in the 42-day risk window following COVID-19 vaccinations as compared to control periods either side of the risk window.

We observed associations between ChAdOx1 adenovirus vector COVID-19 vaccination and ADEM (all dose RI: 3.74 [95%CI 1.02,13.70]) and TM (dose 1 RI: 2.49 [95%CI: 1.07,5.79]) incident admissions. No associations were observed between mRNA COVID-19 vaccines and ADEM or TM. These findings translate to an extremely small absolute risk of ADEM (0.78 per million doses) and TM (1.82 per million doses) following vaccination; any potential risk of ADEM or TM should be weighed against the well-established protective benefits of vaccination against COVID-19 disease and its complications.

This study demonstrates the value of the GVDN collaboration leveraging large population sizes to examine important vaccine safety questions regarding rare outcomes, as well as the value of linked population level datasets, such as VSHL, to rapidly explore associations that are identified.

Introduction

Acute Disseminated Encephalomyelitis (ADEM) is a rare inflammatory neurological disorder of the brain and spinal cord, characterised by inflammation that damages myelin. Also referred to as post-infectious encephalomyelitis, ADEM is most commonly preceded by an acute respiratory or gastrointestinal illness [1]. Typically, multifocal and monophasic ADEM impacts young and adolescent children, with a mean age of six years. ADEM affects both sexes, with a mild male predominance [1]. The estimated incidence of ADEM in childhood ranges from 0.2 to 0.8 per 100,000 per year [1], [2].

Transverse myelitis (TM) is an acute, focal inflammatory myelopathy, that is not associated with encephalopathy, and is clinically characterised by paralysis, sensory impact and autonomic dysfunction below the level of the lesion [3]. Like ADEM, TM is an autoimmune phenomenon that is often preceded by an acute infection [4]. While both conditions predominantly affect children and adolescents, they can occur at any age. Affected children are slightly older than those affected by ADEM, with a mean age at onset of 9–12.6years and a bimodal age peak described [1], [4]. Estimated incidence has been reported as 0.2 per 100,000 per year [1].

ADEM and TM are immune mediated disorders within the group of acquired demyelinating syndromes. Both have been described in temporal association following various vaccinations in case reports and case series and have been evaluated in observational vaccine safety studies [5], [6]. Establishing causality for

such rare events is problematic, and to date, no clear evidence of increased risk of ADEM or TM following vaccination has been established [5], [6].

The life-saving global implementation of COVID-19 vaccines has resulted in more than 13.5 billion doses being administered worldwide by November 22, 2023 [7]. ADEM was included by the international Center for Epidemic Preparedness and Innovation (CEPI) Safety Platform for Emergency vACcines (SPEAC) Project as one of the 37 adverse events of special interest (AESI) to monitor for following COVID-19 vaccination, based upon theoretical concern relating to immunopathogenesis [8].

Recent systematic reviews examined the potential association of different COVID-19 vaccines with the development of ADEM. Nabizadeh *et al.* identified twenty case studies with a total of 54 cases, with symptom onset ranging from 12 h to 63 days (median 14 days) following vaccination. Their findings regarding a causal association were inconclusive and suggested that further population-wide studies be undertaken to investigate potential associations [9]. A separate systematic review by Stoien *et al.* identified 29 ADEM cases following COVID-19 vaccination, and 45 cases following SARS-CoV-2 infection [10].

The Global Vaccine Data Network (GVDN) is an international investigator led collaboration that aims to facilitate collaborative studies of vaccine safety and effectiveness using large-scale health data from diverse populations in countries around the world [11].The Global Covid-19 Vaccine Safety study (GCoVS) was established by GVDN following funding from the U.S. Centers for Disease Control in 2019 to characterise real world safety of COVID-19 vaccines used in at least 34 countries across the world in varying schedules, leveraging large population size to help answer questions regarding rare AESI. GCoVS included ADEM and TM as AESI for background rate determination and as part of signal detection observed/expected (O/E) analyses [8]. As part of these O/E analyses, an excess of both ADEM and TM cases were observed following the adenoviral vectored ChAdOx1 nCoV-19 (AZD1222) and mRNA-1273 vaccine, compared with historically expected background rates from prior to the pandemic [12]. As many factors may cause an excess of observed cases, including association with circulating SARS-CoV-2 infection, we conducted further analyses in large-linked database systems to explore these potential associations.

Section snippets

Methods

We utilised an Australian vaccine datalink, the Vaccine Safety Health-Link (VSHL), to perform a self-controlled case series analysis for this purpose. VSHL provides a repository of linked immunisation, hospital, mortality, perinatal and notifiable condition records occurring in Victoria, Australia, with a population of approximately 6.7 million [13]. These records contain rich demographic and medical information to support rapid and sensitive investigation of vaccine safety concerns with low…

Results

In the dataset from 1 January 2017 to 1 October 2023, 141 cases were admitted to hospital with a total of 279 ADEM events and 417 cases were admitted to hospital with a total of 831 TM events (an average of 2.0 events per person for both conditions). After applying the 365-day outcome washout and restricting to cases in the 1 January 2021 and 1 October 2024 study period, this reduced to 59 ADEM cases with a total of 60 events and 175 TM cases with a total of 178 events (Fig. 1). The 37…

Discussion

The self-controlled case series analysis identified an increased risk of ADEM occurring in the 42-day risk window following vaccination with the adenoviral vectored ChAdOx1 nCoV-19 vaccine. Further, dose-specific analysis suggests that dose 1 may be associated with ADEM and TM more broadly. No increased risk was observed following mRNA BNT162b2 vaccine administration, with insufficient cases following mRNA-1273 to adequately assess the association. These results support the finding of the GVDN…

CRediT authorship contribution statement

Hannah J. Morgan: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Writing – original draft, Writing – review & editing. **Hazel J. Clothier:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Gonzalo Sepulveda Kattan:** Conceptualization, Investigation, Methodology, Formal analysis, Writing – review & editing. **James H. Boyd:** Conceptualization, Investigation, Methodology, Resources, Supervision, Writing – review & …

Declaration of competing interest

The authors 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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