Feedback from operational stakeholders who manage or respond to outbreaks is that they are often too busy to review literature or obtain relevant background information to assist them with acute response. Unlike a traditional analytical outbreak investigation report, ***Watching Briefs*** *are intended as a rapid resource for public health or other first responders in the field on topical, serious or current outbreaks, and provide a digest of relevant information including key features of an outbreak, comparison with past outbreaks and a literature review. They can be completed by responders to an outbreak, or by anyone interested in or following an outbreak using public or open source data, including news reports.*

Watching brief

Title	Report on the 2018 Acute Flaccid Myelitis Outbreaks in the USA
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Date of first report of the outbreak	28 August 2018
Disease or outbreak	Acute Flaccid Myelitis (AFM)
Origin (*country, city, region*)	Multistate, USA
Suspected Source (specify food source, zoonotic or human origin or other)	Non-polio enteroviruses EV-A71 and EV-D68 (1, 2)
Date of outbreak beginning	The exact date of outbreak onset is not publicly known. There have been sporadic cases of AFM reported in the US since February 2018, however data provided by the Centres for Disease Control and Prevention (CDC) suggests that an increase in reported AFM cases occurred in late August 2018 (3, 4). Late August as a possible date of outbreak beginning is supported by an October 10th statement from the Washington State Department of Health describing an initial cluster of five AFM cases with symptom onset dated August 28, 2018 (5). Supporting this, the CDC later confirmed that an increased number of reports for suspected AFM were received with symptom onset dates during August, September, and October (3).
Date outbreak declared over	N/A - Ongoing as of 28 December 2018.
Affected countries & regions	The CDC is reporting at least 38 US States with confirmed AFM cases reported since the beginning of 2018 (4). Of the 341 suspected cases

	reported since February, 186 have been confirmed as of December 28th 2018 (4). A comprehensive list of states affected with individual counts since February can be seen here: https://www.cdc.gov/acute-flaccid-myelitis/afm-surveillance.html It remains difficult to determine whether state-wise totals reported by the CDC comprise sporadic cases reported prior to late August (the apparent onset of the epidemic wave) or as part of the epidemic. Confirmation of cases reported during the epidemic are also uninformative as large numbers of suspected cases could have onset dates between February and August, and individual case data are not described. Public reporting, however, implicates at least seven states in the epidemic wave beginning in late August which could have seeded other states previously reporting sporadic cases prior to August. These include: 1. Washington (5) (10 confirmed) 2. Illinois (6) (9 confirmed) 3. Colorado (7) (16 confirmed) 4. Minnesota (8) (10 confirmed) 5. New Jersey (9) (10 confirmed) 6. Pennsylvania (10) (9 confirmed) 7. Ohio (11) (12 confirmed)
Number of cases (specify at what date if ongoing)	As of December 28, there have been 341 suspected cases of AFM reported since the beginning of 2018. Only 186 cases have been clinically confirmed, with an unknown number still under investigation. At least half of these confirmed cases have been reported between late August and November 2018 (3, 4).
Clinical features	AFM is a clinical syndrome that principally includes a sudden onset of acute limb weakness or paralysis (12). Other features of AFM include difficulty breathing, ataxia (unsteady walking), wobbliness, headache, stiff neck, dizziness and jerking movements (12). Fever can also be expected in 50% of cases (13). Confirmation of AFM requires clinical evidence of "*acute flaccid limb weakness"* and "*evidence of spinal cord lesions*" within the grey matter as shown by Magnetic Resonance Imaging (MRI) (14). Evidence of increased white blood cell count within the Cerebrospinal fluid (CSF) may also be supportive, but not confirmatory, of AFM (15). In the current outbreak, the CDC confirmed that 78% of cases confirmed prior to November 2nd (N=62/80) had respiratory symptoms such as cough, runny

	nose and congestion, 81% (N=65/80) had fever, and 38% (N=30/80) has gastrointestinal symptoms (1).
Mode of transmission (dominant mode and other documented modes)	AFM as a clinical syndrome may be caused by different pathogens and cannot itself be transmitted from person-to-person. Infectious causes of AFM include polio virus, non-polio enteroviruses EV-A71 and EV-D68 (12), some flaviviruses, adenoviruses type 21, and some herpesviruses including cytomegalovirus and Epstein-barr virus (12, 16, 17). Non-infectious causes may include environmental toxins or genetic disorders (17). Transmission of EV-A71 is by the faecal-oral route, however the virus is also present and can transmit via respiratory secretions such as nasal mucus (18). EV-D68 has only recently been associated with AFM (19, 20), and is primarily transmitted via the respiratory route and respiratory illness is the main clinical syndrome for EV-D68 infection (21, 22). EV-D68 has been detected in faeces of some infected cases but faecal-oral route transmission has not been established like EV-A71 (23). Both EV viruses can survive on surfaces as fomites (24, 25). Other known causes of AFM include West Nile, Saint Louis encephalitis, and Japanese encephalitis viruses, which are all mosquito-borne flaviviruses and are primarily carried by Culex spp. mosquitoes (26). Adenovirus transmission is similar to EV-D68, primarily via respiratory secretions. However, unlike EV-D68, transmission via the faecal-oral route has been shown (27).
Demographics of cases	The exact demographics of all cases in this outbreak are not publicly known. The CDC has reported that among cases confirmed prior to November 2nd, 59% (47/80) were male (1). The median age of cases is 4 years (1). This is consistent with the consensus among reporting media indicating that 90% of cases affected are aged under 18 years (28). In the August-November epidemic wave, all cases in Washington are aged under six years (5), all cases in Minnesota are under 10 (8), and all cases in Illinois are under the age of 18 (6). In Colorado, Pennsylvania, and Ohio, all cases are described among “children” (7, 11, 29). There are no details on the cases in New Jersey yet.

Case fatality rate	There has been one suspected death from AFM diagnosed in May 2018, however the CDC has yet to confirm this (30). In the current epidemic wave, starting in August, no fatalities have been confirmed or reported.
Complications	Mild cases of AFM can expect to fully recover, however at least half of cases may have residual limb weakness requiring ongoing physical therapy (31). Severe cases of AFM may experience respiratory failure and require ventilator support (12). Rare neurological complications associated with AFM can sometimes lead to death (12). Long-term complications include paralysis and residual limb deficits.
Available prevention	The causes of AFM are varied and include both infectious and non-infectious aetiologies. As such, the CDC recommends a variety of prevention strategies including: staying up-to-date with vaccines, basic hygiene i.e. washing your hands, and protecting yourself from mosquito bites (4). Of the known causes of AFM, there are no commercially available vaccines for EV-A71 (18), EV-D68 (21), Saint Louis Encephalitis virus (32) or West Nile virus (33) in the US. A vaccine is available to prevent Japanese Encephalitis virus, however it is only recommended for travellers visiting endemic countries for longer than one-month and not available for infants under two months of age (34).
Available treatment	There is no available treatment for AFM, which is limited to supportive care only. This includes the use of assisted ventilation when necessary (12). Specialists may assist with physical therapy whilst hospitalised to reduce muscle weakness or loss (12). The antiviral Fluoxetine has been trailed as treatment for presumptive EV-D68 associated AFM. However, it was not associated with improved outcomes (35).
Comparison with past outbreaks	In recent times, large outbreaks of AFM were first documented in the US in 2014. In the 2014, 120 cases of AFM were confirmed across 34 states between August and December in the US (36). This AFM outbreak was temporally and geographically coincident with large clusters of severe EV-D68 infections. A second outbreak of AFM was reported two years later in 2016 in the US, with 149 confirmed cases across 39 states including the District of Columbia, again coincident with reports of large EV-D68 detections. Application of the Bradford-Hill criteria concluded for the first time that EV-D68 was the likely the cause of the 2014 AFM outbreak (19, 20). In each intervening year, in 2015 and 2017, sporadic cases of AFM have been reported: 22 confirmed cases across 17 states, and 33 confirmed cases across 16 states respectively.

Unusual features	Unlike previous AFM outbreaks associated with EV-D68, this outbreak has been associated with both EV-A71 and EV-D68. Among 125 confirmed AFM cases tested, 21 (42%) have tested positive for EV-A71, 16 (32%) positive for EV-D68, and 13 (26%) positive for other viruses types included rhinovirus A subtypes and Coxsackie A viruses (1). In some states, one species appears to predominate, such as in Colorado, where among 16 AFM cases, 11 tested positive for EV-A71, one for EV-D68, and two negative for enterovirus species (7).
Critical analysis	Since 2014, there have been 512 confirmed cases of AFM in the US (4). To-date, this is the largest outbreak of confirmed AFM in the US. The incidence of reported AFM has increased every two years since 2014 in the United States. Surveillance data shows 120 cases of confirmed AFM reported in 2014, 149 confirmed in 2016, and 193 in 2018 confirmed so far (3, 4). The number of states implicated in each outbreak has also increased from 34 in 2014 to 39 in both 2016/18 (3). Reporting of AFM however remains voluntary in the US so the true incidence remains unknown. The clinical similarity of AFM to other neurologic syndromes, e.g. Guillain-Barré syndrome and idiopathic transverse myelitis, increases the chance of misdiagnosis, potentially concealing the true AFM incidence further (37). Interestingly, the onset of the 2018 outbreak coincides with time-of-onset observed in both previous outbreaks in 2014 and 2016: August to October (4). This suggests a two-year cyclical dynamic of AFM outbreaks and a seasonal pattern is emerging, meaning another outbreak in August 2020 might also be expected. This cyclical dynamic also supports the role of a viral agent as the cause of the 2018 outbreak rather than unknown sporadic or environmental cause, such as a toxin. Supporting this conclusion, the CDC released a report on 16 November 2018 based on the results of early diagnostic testing stating "*clinical, laboratory, and epidemiologic evidence to date suggest a viral association*" (1). Among 125 confirmed AFM cases tested, 21 (42%) have tested positive for EV-A71, 16 (32%) positive for EV-D68, and 13 (26%) positive for other viruses types, including rhinovirus A subtypes and Coxsackie A viruses (1). Detection in the cerebrospinal fluid (CSF) is confirmative of the pathogen being the cause of AFM, however only two AFM cases among 21 specimens tested positive: one EV-A71, and another for EV-D68. While these numbers are limited, it is rare that EV-D68 and EV-A71 are detected in the CSF, even among cases with confirmed AFM and positive respiratory or stool samples. For example, in the 2014 outbreak, of the 120 confirmed AFM cases, only 12 had confirmed EV-D68 infections, 11 from respiratory samples, and one from CSF (19, 38). This is likely due to the limited replication and persistence of EV virions in the CSF (20, 39, 40) and the delay between symptom onset and specimen sampling as observed in the 2014 outbreak (38) .Therefore, while CSF positive detections are confirmatory, negative CSF results does not

	weaken other clinical and diagnostic evidence for EV-A71 and EV-D68 aetiology. Due to the emergence of EV-D68 as a likely cause of the 2014/16 AFM outbreak in US, it is possible that EV-D68 may be the cause of the 2018 outbreak. Clinical and diagnostic evidence provided by the CDC above supports this conclusion. Perhaps unusual in this outbreak is the simultaneous detection of EV-A71 among many AFM cases. Detection of EV-A71 in previous AFM outbreaks in the US is not known. In 2014, 11 Non-EV-D68 enterovirus species were detected in the stool of AFM cases, suggestive of EV-A71 infection as a faecal-oral pathogen but was not specified (38). In 2016, a single AFM case in Washington State tested positive for EV-A71 among 10 confirmed AFM cases (37). Similarly, there is little evidence internationally for co-circulation of EV-D68 and EV-A71 among AFM cases. For example, in France, enterovirus-associated AFM appears mostly associated with EV-A71, although EV-D68 has been detected previously in a single case (41). Of all the 38 states affected, Texas has recorded the most AFM cases (n=25), followed by Colorado (n=16). Based on public data and reporting, we cannot determine if the majority of confirmed cases in Texas had onset dates during the epidemic period August to October, or prior. In September, a Morbidity and Mortality Weekly Report (MMWR) was published describing an increase in EV-A71 associated encephalitis, meningitis and AFM in Colorado between May 10 and June 5, 2018 (42). During this period, 34 young children (<2 years) presented with neurological symptoms and tested positive for EV-A71; three were subsequently classified as AFM (42). In the current epidemic which began in August, of the 16 positive AFM cases, 11 have tested positive for EV-A71 (7). Only one cases has tested positive one for EV-D68, while two have tested negative for enterovirus species (7). This might suggest EV-A71 is the predominate cause of the current AFM outbreak in Colorado, while EV-D68 is only a minor cause there. In 2014, like 2018, Colorado was also one of the first states to report an increase in AFM detections (43). This suggests Colorado may be a significant state for the emergence of AFM epidemics in the US. It is unclear if other states also experience simultaneous emergence of AFM or if a single state such as Colorado may act as a source, potentially disseminating the disease across the US. If the emergence is simultaneous, the environment and seasonality of non-polio enteroviruses may provide one explanation. Non-polio enteroviruses are known to circulate all-year round, however peaks typically occur in summer between July and September in the Northern Hemisphere (44). Outbreak timing and transmission intensity has been shown to be associated with latitudes and dew-point temperatures such that northern states observed peaks later in the season whereas southern states observed a regular distribution of cases throughout the year. This supports the case for non-polio enteroviruses as the cause of the current AFM outbreak as most states affected since August epidemic wave are located in the Northern US:

	Washington, Illinois, Colorado, Minnesota, New Jersey, Pennsylvania, and Ohio (5-8). Clusters of EV-D68 have also been reported in New York, however none of these cases have exhibited symptoms associated with AFM (45). Other evidence suggests non-polio enterovirus seasonality may be driven by a waning of seroprevalence in the population and the emergence of immunologically naïve newborns (46). The detection of 13 non-enterovirus species among AFM cases (1) means other known viral aetiologies might also be implicated, including rhinovirus A subtypes and Coxsackie A viruses, however they do not have a history of neurological invasion and AFM. Likewise, symptomatic evidence can exclude flaviviruses previously associated with AFM such as West Nile Virus, which typically present with skin rash, as the cause of this AFM outbreak. Furthermore, diagnostic testing for flaviviruses require blood samples, which if taken, have not been publicly reported. Adenoviruses type 21 (AD21) has also been associated with AFM in the past (16). A large outbreak of Adenovirus has sickened 36 in New Jersey between September and November, which has temporal and spatial associations with current AFM outbreaks also in New Jersey (9, 47). Eleven deaths have been implicated in this Adenovirus outbreak, however no cases have developed AFM and the dominant clinical syndrome was reported to be respiratory illness (48). Typing has also shown a mix of adenoviruses types 3 and 7 predominating in the New Jersey outbreak, which do not have a history of causing AFM (48). This might practically eliminate AD21 as a potential cause of the current AFM outbreak.
Key questions	What is the cause of AFM in the US in 2018? Why is AFM increasing in the US? Is Colorado a key state for the emergence of AFM epidemics in the US or is the seasonality of non-polio enteroviruses a key predictor? Is EV-D68 or EV-A71 the primary cause of this AFM epidemic, and if so, how common is it for two different co-circulating viruses to cause a single outbreak? Is there common factor among all cases with positive and negative enterovirus results? Is there another non-enterovirus related cause to this outbreak? Could Rhinovirus A and Coxsackie A viruses be a new cause of AFM? Can we exclude flaviviruses (West Nile, Saint Louis encephalitis virus, and Japanese encephalitis virus), other adenoviruses or a new pathogen?

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