# ESSAY: AESI'S ASSOCIATED WITH COVID-19 VACCINES

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# Introduction

## Corona: clinical

In 2020, the global medical community is struggling with a new coronavirus called SARS-CoV-2. This virus causes COVID-19 and first cases were reported already in December 2019 in Wuhan, China. COVID-19 causes in general flu-like symptoms, sometimes feverish symptoms are also occurring. In severe cases, immediate medical care is needed. 20 Per cent of COVID-19 patients require medical care and help, in some cases medical oxygen supply or intensive care. These patients often suffer from complications that are linked to organ damage and may lead to death. Vulnerable patients are also likely to be over 60 years and have underlying medical problems like high blood pressure, heart and lung problems and obese and have lifestyle diseases. Long-term effects are possible in all patients of COVID-19 and include fatigue, respiratory and neurological symptoms. It is not clear who will experience long-term effects and how long they persist. [1]

This is alarming since it is also not predictable how long the second wave will persist. Experts of RIVM (Rijksinstituut voor Volksgezondheid en Milieu, so National Institute for Public Health and the Environment of the Netherlands) suppose that the second wave will be over in March of 2021, since the uncertainty remained unchanged in previous months. [2]

However, it is to be expected that vaccines will lead to a decline of new cases and therefore a shortening of the wave. Vaccinating is after all an effective and important technique for prevention. The European Commission has purchased six different type of vaccines for the Netherlands. Two of them are likely to be available at the end of 2020. These vaccines, manufactured by Pfizer and AstraZeneca, have shown to be of great efficacy ( above 90 per cent) in trial III studies. However, the availability of these vaccines will be limited in the Netherlands initially since the vaccines will be divided over several European countries according to European resolution. The first grant of vaccines for the Netherlands is estimated at 10.000. Therefore, a strategy has to be outlined. The Dutch Health Council has advised to vaccinate the elderly and risk groups first.

What we do not know are the risks in rare in severe side effects of vaccination. The vaccines are so far only tested in about 40 to 50 thousand volunteers. So there are concerns about safety when vaccination is nationally implemented. These concerns are grounded since rare adverse events and those with a long time to onset are not likely to occur in trial III studies. [3]

Therefore Postmarketing Surveillance is needed. Background rates of syndromes are necessary to assess the safety of vaccines and medicines after authorization. In the past, several associations between those adverse events and vaccination were reported. This specific type of adverse event is called Adverse Event of Special Interest (AESI). The association could be based on an increase in incidence of an AESI after vaccination programme. The manufacturer and sponsor of the vaccine or medicine is responsible for surveillance, monitoring and communication of AESIs. After all, AESIs may affect the vaccination programme. [4]

It is presumed that AESIs related to COVID-19 could include respiratory and cardiac injury, Guillain Barré Syndrome and Multisystem Inflammatory Syndrome in Children. Some of these outcomes are actually vaccine-enhanced diseases. [5]

Guillain Barré Syndrome and Multisystem Inflammatory Syndrome in Children are outlined in this article.

### Epidemiological data and literature collection

Primarily, Uptodate was consulted for clinical and general information about the AESIs. Therefore, the name of the AESI was entered in the search bar. If no sufficient information was provided, then PubMed or Elsevier Sciencedirect was consulted. Sometimes Uptodate also provided information and data about epidemiology. Then the original article was assessed but sometimes the epidemiological claims seem to be invalid. Therefore some articles were found with again PubMed, Elsevier Sciencedirect, or The Lancet or another journal. For this, sometimes it was necessary to add more keywords like epidemiology or prevalence or incidence.

## Results

A number of AESIs associated with vaccines

<u>Erythema multiforme</u>

Erythema multiforme (EM) is an immunological condition, actually a hypersensitivity reaction that is characterized by cutaneous lesions and sometimes on mucosa. In general, these lesions can be found on hands and feet and look like red maculae (rashing). There are two types of EM: EM major (with mucosal lesions) and EM minor (without mucosal lesions). The occurrence can be incidental, recurrent or permanent. EM is mostly caused by infections (about 90%) especially Herpes simplex virus and Mycoplasma pneumoniae (mostly in children). Specific medications (<10% of cases, in children >10%), malignancy, radiations, menstruation, immunizations and autoimmune diseases also tend to develop ME. Different classes of medications like nonsteroidal anti-inflammatory drugs, sulfonamides, antiepileptics, and antibiotics are known to induce EM. The general development of ME is transient, takes three to five days and within about two weeks recovery is completed. In many cases the skin does not show scars. However, post-inflammatory hyperpigmentation may occur and this lasts for months after recovery, especially in dark skinned patients. As mentioned earlier, there are different occurrences so their courses are also different. Recurrent EM appears frequent times over many years; in average there are six episodes annually with mean duration from six to ten years. Permanent EM is characterized by persistent occurrence of different EM lesions and they are often widespread. [6]

The annual incidence is estimated to be less than 1 per cent, the actual incidence rate is not known due to the absence of international or global handled classification system. There is also no reporting registry perhaps because of the acute nature of EM. It is slightly more common in females than in males, namely 1,5 times more.

It is also more common in young adults, namely between 20 and 40 years. 37 per cent of all cases has the recurrent type, and certain Asian ethnic groups are genetic vulnerable. Mortality rates of EM are not known, since they are not well documented. [7]
However, EM is possible in all ages and one out of five cases is seen in children. [8]

| Syndrome | Study | Population | Patient characteristics | Incidence / prevalence (range) | Type of study | Remarks |
|---|---|---|---|---|---|---|
| **EM** | Samim et al. [7] | Populations from several parts of the world | Hospitalized patients | 0,4 to 39,9 per 1 million Annual Incidence Rate of EM Group Requiring Hospitalization | Systematic review | Different study periods |
| | Heinze et al. [9] | Children (below 18 years) from the Children's Hospital of Wisconsin in Milwaukee | diagnosis before age 18 years with recurrent EM | 16 of 26 patients were male (62%), 9 patients required hospitalization (35%) Herpes simplex was found in 65% of patients (9 of 17) | Retrospective chart review (1990-2015) | Differences in epidemiology between general population and examined children are found. |

## Guillain Barré Syndrome

Guillain Barré Syndrome (GBS) is an umbrella term for various acute immune-mediated polyneuropathies. This syndrome is in general characterized as an induced acute monophasic paralysis by a prior infection. These infections are most commonly caused by Campylobacter jejuni, followed by cytomegalovirus (CMV), Epstein-Barr virus (Pfeiffer's disease), Human immunodeficiency virus (HIV) and Zika virus. GBS might also occur after vaccination, surgery, trauma and bone marrow transplantation. GBS is believed to be a consequence of an immune response to a prior infection that has a cross-reaction with particular nerve components due to molecular mimicry. [10]
It is not clear if other factors like genetics and environment affect are risk factors for developing GBS. The key feature of GBS is muscle weakness along with decreased or absent tendon reflexes. This weakness is progressive and appears symmetrically from the limbs (usually legs) and gradually ascents to the torso and eventually to the central nervous system. This phase is known as progression and this acute weakness leading to paralysis and peaks within 4 weeks. About 25 per cent of patients has ventilatory muscle injury and therefore needs artificial ventilation. Luckily, recovery is possible although this takes months or in some cases years. Poor recovery is also possible and this is characterized with pain, fatigue and decreased physical or mental capacities and output. [11]

GBS is a rare disease, occurring in less than 1 (0,8) to 2 (1,9) cases out of 100.000 persons per year, according to most studies done in North America and Europe. This syndrome occurs slightly more in males than in females. Seasonal fluctuations may theoretically affect incidences due to variations in infectious pathogens, but they seem rarely statistically significant. Besides, geographical variations in incidence are also

known due to local infectious habitats, leading to perceived outbreaks. Lifetime risk of developing GBS is estimated to be less than 1 in 1000. [11]

Besides, there is a possible association between COVID-19 and GBS. In several healthcare centres patients with GBS were found to have active or resolved COVID-19. From other coronaviruses is known to affect the central nervous system, examples of pathologies are toxic infectious encephalopathy and viral encephalitis. [12]

| Syndrome | Study | Population | Patient characteristics | Incidence / prevalence (range) | Type of study | Remarks |
|---|---|---|---|---|---|---|
| **GBS** | Sejvar et al. [13] | Populations from several parts of the world | patient number > 20 per study, population-based data | Incidence between 0,8 and 1,9 per 100.000 person years. Age specific ranges in incidence also found. | Systematic review | Different case definitions and identifications |
| | Gittermann et al. [12] | 30 cases worldwide | 14 patients were men, 11 were women and 5 patients had unknown gender and age. Age range was 43-76 years. | 2 Deaths were reported. False negative PCR test for SARS-CoV-2 was found in 3 cases | Systematic review | All patients tested negative for SARS-CoV-2 in the cerebrospinal fluid (CSF). |

Multisystem inflammatory syndrome in children

Multisystem inflammatory syndrome in children (MISC) is an immunological disease only occurring in children. This paediatric disease is thought to be an overreaction of the immune system. Especially after COVID-19 infection this disease has been gained attention, since more cases were reported. Even when a child was asymptomically infected with SARS-CoV-2 he or she could still develop MISC. MISC has six characteristics: paediatric age, continuous fever, increased levels of inflammation markers, signals of organ dysfunction/failure, no other diagnosis and previous exposure or infection of COVID-19. However, MISC has still to be defined clearly. MISC is a severe disease including hyperinflammatory shock and cardiac dysfunction.
Risk factors are not fully known but some ethnic groups (for example African and Hispanic) seem to have an association with MISC. Also children who are overweight or obese have a higher risk of developing MISC since they are more vulnerable for the COVID-19 virus. [14]
It is obvious that MISC patients are hospitalized and almost 3 out of 4 children were treated in intensive care (from 39 studies, n = 662 patients). The mean length of hospitalization was 7,9 days with 0,6 days as standard deviation. Typical symptoms were fever (100%), diarrhoea (73,7% n = 488) and vomiting (68,3, n = 452). Abnormal markers were found for serum inflammation, coagulation and the heart. From 662 patients, the mortality rate was 1,7% (n = 11). [15]

The incidence of MISC is unknown, since it is a new and a rare phenomenon among children. MISC shows great similarities with Kawasaki disease, this disease is better

understood and also the association between Kawasaki disease and COVID-19 was studied. First reports concerning MISC are from UK in April 2020. The first report was a case series of eight children in a tertiary hospital in South East England. Following case series were again from the UK but also from the US. More than 70 per cent of the patients were healthy before and the median range was from 8 to 11 years with a range of 1 to 20 years. Reports from other parts of the world about similar condition were followed and in one report from the US the estimated incidence of MISC below 21 years was 2 per 100.000 while the incidence of SARS-CoV-2 was 322 per 100.000. These numbers were obtained from hospitals in collaboration with New York State Department of Health between 1 March and 10 May 2020. [16]

In the Netherlands, children with COVID-19 are registered in hospitals and are included in so-called COPP-study. These children may stay for secondary or tertiary care. This study is carried out by LUMC (Leiden Universitair Medisch Centrum), Dutch Pediatric Trial Network Radboudumc Nijmegen and NVK (Nederlandse Vereniging voor Kindergeneeskunde). This study is in collaboration with paediatricians and investigates the course and risk factors of severe COVID-19 in children who are seen or stayed in the hospital. MISC is also investigated in this study. Provisional data and results are presented on the dashboard and these are automatically generated. This dashboard consists of various graphs and diagrams; data on MICS is also shown. About 8 to 9% of COVID-19 children have MICS and inflammatory syndrome is seen in less than 10 children in 2020, 4 boys and 5 girls are or were suffering. The ages of the children are also known. The youngest patient is a boy of 0 to 2 years. Other boys have the age of 10 to 12, 12 to 14 and 14 to 16 years. Three girls have the age of 6 to 8, 8 to 10 and 10 to 12 years. Other two girls have the age of 16 to 18. The most common symptoms of MISC in these children are fever, nausea and abdominal pain. [17]

| Syndrome | Study | Population | Patient characteristics | Incidence / prevalence (range) | Type of study | Remarks |
|---|---|---|---|---|---|---|
| **MICS** | Riphagen et al. [18] | Children from South East England, hospitalized | 6 of 8 children were of Afro-Caribbean descent, 5 of 8 were boys and 7 of8 were overheight | 8 out of 2 million children in South East England | Case series | Other children had no Caucasian descent (one Middle-Eastern and one Asian) |
| | Feldstein et al. [19] | Children from 26 States of America | 186 patients. 115 so 62 % were boys and 73% were previously healthy | 148 children so 80 % received intensive care, 4 children died so 2% | Targeted surveillance | Case definition included 6 criteria |
| | Dufort et al. [20] | Children from hospitals in New York State | 95 children of 191 potential cases had conformed MISC and 4 children had suspected MISC | Estimated incidence of MISC below 21 years was 2 per 100.000 | Tageted surveillance, statewide | Similar diseases were also reported |
| | Buddingh et al. [21] | Children in the Netherlands, COPP-study | 9 children are known to have MISC | Less than 10 % of COVID-19 | Targeted surveillance, nationwide | Long-term effects of |

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| | | | | children has MISC | | COVID-19 are also examined. |

Narcolepsia:

Narcolepsia is an unusual sleep disorder, there is a disturbance in sleep-wake control. This gives excessive and irresistible drowsiness, also in daytime. Other features are cataplexy (acute muscle weakness due to intense emotions), hypnagogic hallucinations (vivid dreams at the beginning of sleep) and sleep paralysis (inability of movement when falling asleep). This neurologic disorder is seen in adults and in children and can present at very young age (4 or 5 years). However, some cases are lately diagnosed since paediatric features are not matched with those of adults. Narcolepsy is a lifelong disorder. According to the International Classification of Sleep Disorders, Third Edition (ICSD-3), there are two types of narcolepsy:
Type 1: Narcolepsy with cataplexy and type 2: Narcolepsy without cataplexy.
The distinction between these two types is needed since their pathophysiologies are different from each other as well as their diagnostic criteria. Type 1 may be caused by a deficiency of a neuropeptide called orexin, which is involved in stabilizing wakefulness and preventing the transition of REM to non-REM sleep. This type seems to have a genetic and/or autoimmune predisposition. The aetiology of type 2 is less clear, but certain lesions affecting brainstem may stimulate secondary narcolepsy probably caused by disruption of orexin secretion. Circa 24 per cent of type 2 patients has low orexin levels and half of these patients will develop cataplexy so their disorder is worsened. Other head injuries and sarcoidosis are also associated with secondary paediatric narcolepsy. Some genetic syndromes like Prader-Willi syndrome also present narcolepsy. Narcolepsy does not have a typical age of onset, and about 33 per cent of narcoleptic patients show all four features. Hypnagogic hallucinations and sleep paralysis are seen in just above the half (50 to 60 per cent) of paediatric patients. Cataplexy shows a great variation in frequency, tens of cataplexy episodes in a day may give a clumsy impression of a child but are no exception.
Neuropsychiatric symptoms are more seen in children than in adults, examples are aggressiveness and troubles with concentration. [22] [23]

Type 1 narcolepsy has an estimated prevalence of 25 to 50 per 100.000 people and an incidence less than 1 per 100.000 person-years namely 0,74. Narcolepsy occurs equally among men and women. In general narcolepsy begins at adolescence. Narcolepsy type 2 is less studied and therefore there is less knowledge about the prevalence. The prevalence is thought to be between 20 and 34 per 100.000 people. For children, there are other incidence and prevalence rates. A European study found a pooled incidence of 0,83 per 100.000 children-years (5-19 years) and the children in Western countries have an estimated prevalence of between 20 and 50 cases per 100.000. However, a sudden increase of incidence in children and adolescents was observed in 2009 and 2010. This increase was 3 to 4 fold and found in Europe and China due to the H1N1 influenza A pandemic. Due to unfortunate timing, it was thought that narcolepsia was a result of a mass influenza vaccination program with Pandemrix. It is still not understood what the cause was of this increase. [22] [23]

| Syndrome | Study | Population | Patient characteristics | Incidence / prevalence (range) | Type of study | Remarks |
|---|---|---|---|---|---|---|
| **Narcolepsia** | Longstreth et al. | Patients from various parts of the world | Patients with different clinical features were examined | The average incidence was 0,74 per 100,000 person years between 1960 and 1989 | Systematic review | Diagnosis was defined in different ways |
| | Wijnans et al. [25] | Patients from different countries in Europe | Patients before and after pandemic vaccination | Pooled incidence rate of 0,93 per 100.000 person years was found, 2608 cases of 280 million person years | Dynamic retrospective cohort study | Rate ratios of above 1 were found for narcolepsy before versus after pandemic influenza vaccination |
| | Douvillier's et al. [26] | Children and adults in France | Patients with narcolepsy -cataplexy from 14 expert centres | Odds ratio of 6,5 (2,1– 19,9) was found for H1N1 vaccination associated narcolepsy in children (< 18 years) and 4,7 (1,6 – 13,9) for adults. | Case-control, retrospective | Overall Odds ratio was 5,5 (2,5 – 12,0).<br><br>Matching was based on gender, age and location. |

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