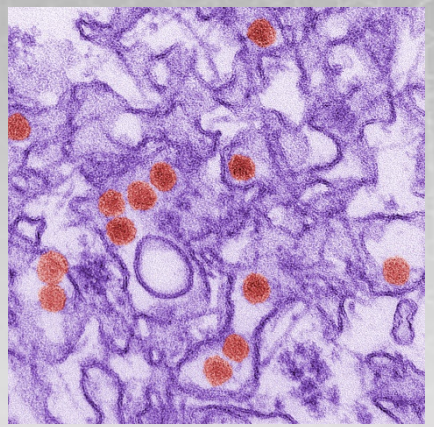
PolyNeuro exchange

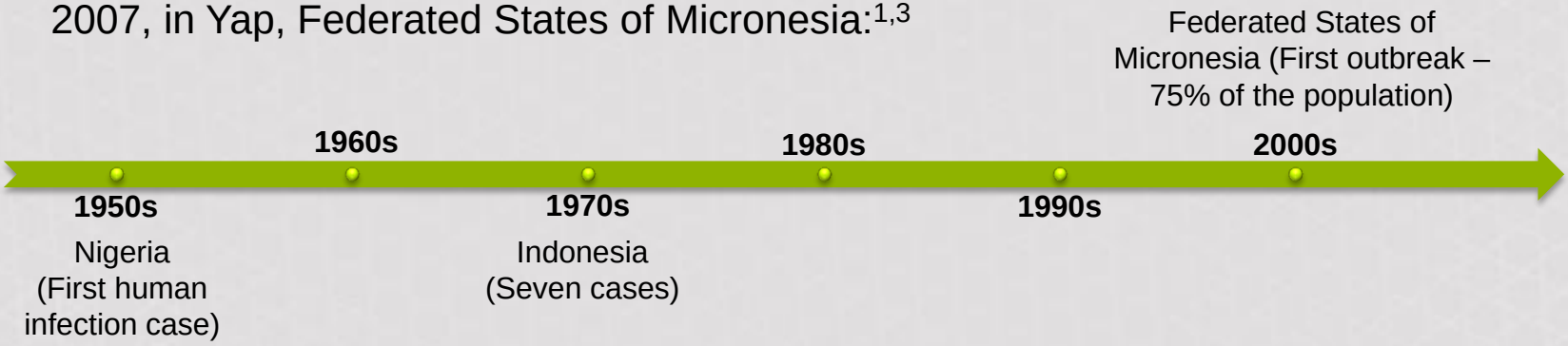
GBS and Zika Virus

Zika virus classification and history

- The Zika virus is an arbovirus of the family Flaviviridae and the genus Flavivirus[1]
  - Zika is an enveloped, icosahedral positive strand RNA virus[1,2]
  - Serologic cross-reactivity, including non-neutralizing antibodies, occurs with other flaviviruses and flavivirus vaccines[2]
  - Other flaviviruses include yellow fever, dengue, West Nile, and Japanese encephalitis viruses[1]
- The virus was first isolated in 1947 from a rhesus monkey in the Zika forest area of Uganda[1]
- Human Zika fever or disease has been recognized since the early 1950s but the first outbreak was only reported in 2007, in Yap, Federated States of Micronesia:[1,3]



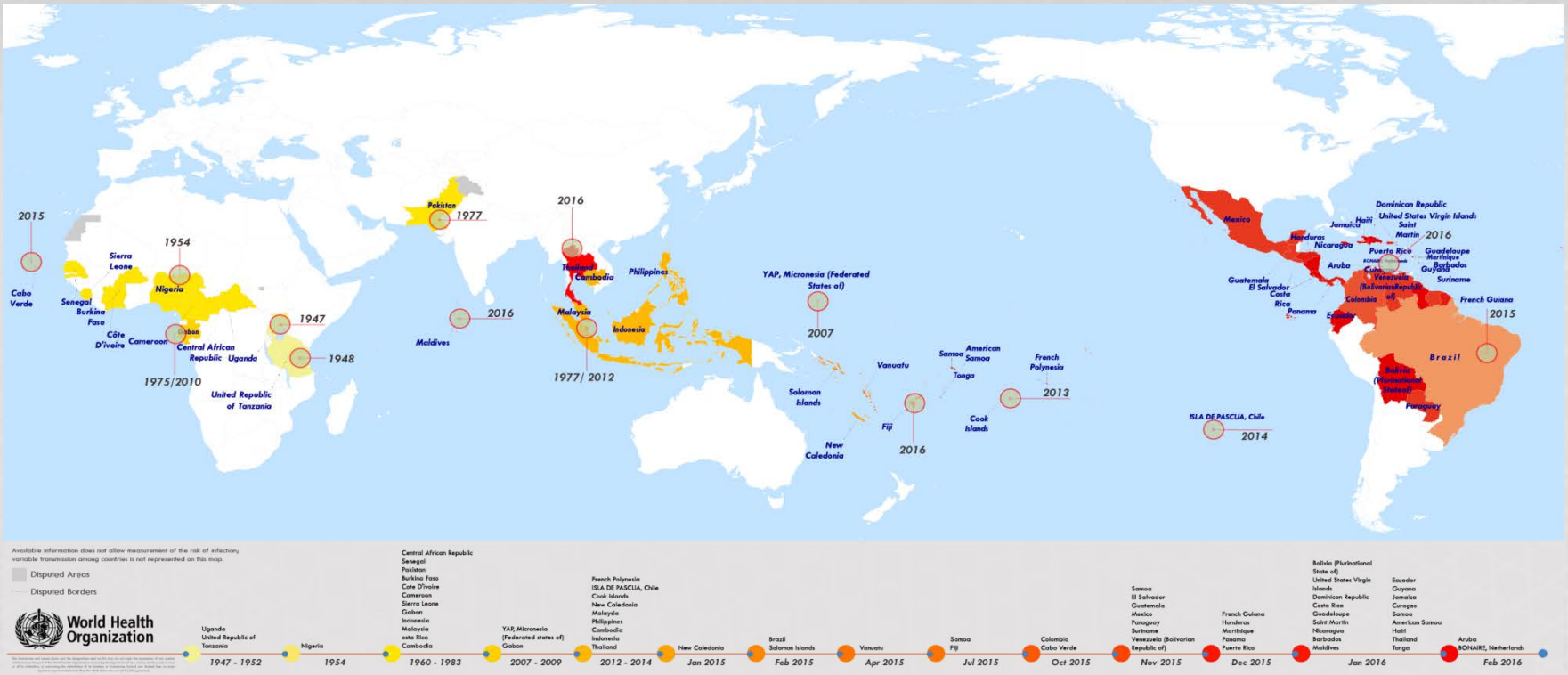
Transmission electron micrograph of Zika virus. Virus particles (shown in red) are 40 nm in diameter, with an outer envelope, and an inner dense core.[4]



1. Chang C *et al.* J Autoimmun. 2016;68:1–13.
2. Malone RW *et al.* PLoS Negl Trop Dis. 2016;10(3):e0004530.
3. Petersen LR *et al.* N Engl J Med. 2016;374(16):1552–1563.
4. Centers for Disease Control and Prevention. Photo credit: James Gathany. Available at: http://www.cdc.gov/media/images/dpk/2016/dpk-zika/zika-virus-microscope-1000px.jpg. Accessed June, 2016.

Geographical distribution of the Zika virus

- Currently, 69 countries have reported mosquito-borne Zika virus transmission and 11 countries reported person-to-person transmission of Zika virus (transmission assumed to be via a sexual route)[1]
- Countries and territories showing historical distribution of Zika virus, 1947–2016:[2]



1. World Health Organization. Zika situation report. Available at: http://apps.who.int/iris/bitstream/10665/249518/1/zikasitrep11Aug2016-eng.pdf?ua=1. Accessed August, 2016.
2. World Health Organization. Available at: http://www.who.int/emergencies/zika-virus/zika-historical-distribution.pdf?ua=1. Accessed June, 2016.

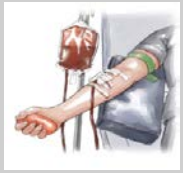
Transmission of the Zika virus: The *Aedes* mosquito

- Zika virus is primarily transmitted through the bite of infected species of the *Aedes* mosquito[1,2]
- *A. aegypti* mosquito is the predominant carrier[1,2]
  - Primarily active during the daytime, and widely distributed throughout tropical and subtropical climates[1,2]
  - High vectorial capacity, feeding primarily on humans[2]
    - Able to bite multiple humans in a single blood meal
    - Almost imperceptible bite
    - Lives in close association with human habitation
  - The mosquito lives for 2–4 weeks, but its eggs can survive for long periods in a dry state[1]
  - This mosquito also transmits dengue, yellow fever, and chikungunya[1]

Aedes aegypti mosquito feeding from a human host (top) and leaving the host's skin surface (bottom).[3]

1. Chang C *et al.* J Autoimmun. 2016;68:1–13.
2. Petersen LR *et al.* N Engl J Med. 2016;374(16):1552–1563.
3. Centers for Disease Control and Prevention. Photo credit: James Gathany. Available at: http://phil.cdc.gov/phil/details.asp?pid=9261 (top) and http://phil.cdc.gov/phil/details.asp?pid=9220 (bottom). Accessed June, 2016.

Transmission of the Zika virus: Non-mosquito transmission

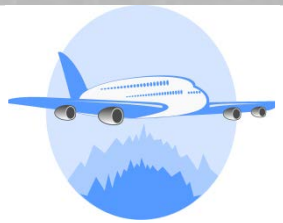
Routes	Description
Perinatal 	• The Zika virus can be transmitted from the mother to the fetus during pregnancy or childbirth[1,2] – There is no evidence that Zika virus can be transmitted through breast milk • Zika virus infection during pregnancy has been associated with: microcephaly, and other severe fetal cerebral abnormalities; eye defects; hearing loss; and impaired growth[2]
Sexual 	• Sexual transmission from both infected male and female partners has been reported[1,3,4] • Although the risk of sexual transmission has not yet been determined, replicative viral particles have been detected in sperm up to 62 days after the onset of symptoms[1,3]
Blood Transfusion 	• Blood transfusion-related transmission of the Zika virus has been reported[5] – Other flaviviruses are known to be transmitted via this route – 3% of donated blood samples during the Zika virus outbreak in French Polynesia tested positive for Zika virus by reverse-transcriptase polymerase chain reaction – To reduce the risk of transmission, donors should be educated on the signs and symptoms of Zika virus infection. Those who have been infected, or have traveled to an area of active transmission of Zika virus, should postpone donating until 4 weeks after their return and inform the blood collection authority if they develop symptoms within 2-weeks post-donation[6,7]

1. Maharajan MK *et al.* Clin Rev Allergy Immunol. 2016;DOI 10.1007/s12016-016-8554-7 [Epub ahead of print].
2. Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/zika/pregnancy/question-answers.html. Accessed June, 2016.
3. Petersen LR *et al.* N Engl J Med. 2016;374(16):1552–1563.
4. Davidson A et al. Available at: http://www.cdc.gov/mmwr/volumes/65/wr/pdfs/mm6528e2.pdf. Accessed August, 2016.
5. Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/zika/transmission/blood-transfusion.html. Accessed August 2016
6. FDA. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM486360.pdf. Accessed June, 2016.
7. America's Blood Centers®. Available at: http://www.americasblood.org/media/59434/joint_statement_-_puerto_rico_shipments_3.9.16.pdf. Accessed June, 2016.

Travel advice[1]

Protect against mosquito bites

- Use insect repellent (containing DEET, IR3535 or icaridin) and sleep under a mosquito net
- Cover exposed skin
- Cover, empty, or clean potential mosquito breeding sites
- Use screens and air conditioning (if available) in homes



Reduce the risk of sexual transmission and potential pregnancy complications related to Zika virus infection

- Sexual partners of pregnant women, living in or returning from areas affected by the Zika virus, should practice safe sex or abstain from sexual activity throughout the pregnancy
- If returning from areas affected by the Zika virus, practice safe sex or abstain for at least 8 weeks after returning, even if asymptomatic
- Men experiencing Zika virus symptoms should practice safe sex or abstain for at least 6 months
- If planning a pregnancy, wait at least 8 weeks before trying to conceive if no symptoms of Zika virus infection appear, or 6 months if one or both members of the couple are symptomatic

1. World Health Organization. Zika virus. Available at: http://www.who.int/mediacentre/factsheets/zika/en/. Accessed June, 2016.

Zika virus infection: Symptoms, diagnosis, and treatment

Symptoms[1,2]

- Typically asymptomatic during initial infection (viremia can begin up to 10 days before onset of symptoms, which is longer than for other arboviruses)
- Acute symptoms include: fever, maculopapular rash, muscle and joint pain, conjunctivitis, malaise, and headache
- Symptoms are usually mild and persist for 2–7 days

Diagnosis[2,3]

- **Suspected case:** presence of rash and/or fever with either arthralgia, arthritis, or non-purulent conjunctivitis
- **Probable case:** suspected case with presence of anti-Zika IgM antibodies and epidemiologic link within 2 weeks prior to symptom onset
- **Confirmed case:**
  - Laboratory confirmation of either Zika virus RNA or antigen in serum or other samples (e.g. saliva, tissues, urine, whole blood); **or**
  - IgM antibody against Zika virus positive and $PRNT_{90}$ for Zika virus with titre ≥20 and Zika virus $PRNT_{90}$ titre ratio ≥4 compared to other flaviviruses; and exclusion of other flaviviruses

Treatment[1,4]

- There are no vaccines or antiviral therapy available
- Usually no treatment is required
- Infected people should rest, drink fluids, and treat pain and fever with antipyretics

1. World Health Organization. Zika virus. Available at: http://www.who.int/mediacentre/factsheets/zika/en/. Accessed June, 2016.
2. Malone RW *et al.* PLoS Negl Trop Dis. 2016;10(3):e0004530.
3. World Health Organization. Zika virus disease. Available at: http://www.who.int/csr/disease/zika/case-definition/en/. Accessed June, 2016.
4. Maharajan MK *et al.* Clin Rev Allergy Immunol. 2016;DOI 10.1007/s12016-016-8554-7 [Epub ahead of print].

Zika virus: Neurological complications

- Zika is a neurotropic virus that primarily targets neural progenitor cells but also neuronal cells in all stages of maturity[1]
- An international public health emergency was declared by the World Health Organization (WHO) on February 1, 2016 due to an unusual cluster of cases of congenital microcephaly and Guillain-Barré Syndrome (GBS) associated with Zika virus infection[1,2]
- Additional congenital manifestations associated with Zika virus include:[1]
  - Craniofacial disproportion
  - Spasticity
  - Seizures
  - Irritability
  - Brainstem dysfunction, including feeding difficulties, ocular abnormalities, and findings on neuroimaging such as calcifications, cortical disorders, and ventriculomegaly
- Cases of encephalitis and myelitis associated with Zika infection have also been reported[3,4]

1. Costello A *et al.* Bull World Health Organ. 2016;94:406–406A.
2. World Health Organization. WHO statement. Available at: http://www.who.int/mediacentre/news/statements/2016/1st-emergency-committee-zika/en/#. Accessed June, 2016.
3. Carteaux G et al. N Engl J Med. 2016;374(16):1595–1596.
4. World Health Organization. Zika situation report. Available at: http://apps.who.int/iris/bitstream/10665/208816/1/zikasitrep_2Jun2016_eng.pdf?ua=1. Accessed June, 2016.

Typical GBS: Description and prevalence

- Typical GBS is an acute, immune-mediated polyneuropathy, affecting all ages, ethnicities, and genders
  - Most common cause of acute, rapidly progressive, generalized limb weakness due to polyradiculoneuropathy, with an estimated annual incidence of approximately 2 per 100,000 people[1–3]
  - More prevalent in men and the elderly[2,3]
- Typical GBS has an acute onset with maximal disability reached within 4 weeks for 90% of patients[1,4]
- The majority of patients report a preceding infection within 6 weeks prior to onset[1]
  - Commonly a flu-like illness, upper respiratory tract infection or gastroenteritis
  - A range of bacteria and viruses can act as triggers for the syndrome
  - *Campylobacter jejuni* is the most commonly identified bacterial infection

1. Hughes RA *et al*. Lancet. 2005;366(9497):1653–1666.
2. van Doorn PA *et al*. Lancet Neurol. 2008;7(10):939–950.
3. Shui IM *et al.* Neuroepidemiol. 2012;39(2):109–115.
4. Asbury AK, Cornblath DR. Ann Neurol. 1990;27(suppl):S21–24.

Diagnostic criteria for typical GBS[1,2]

Clinical features

- Progressive weakness in both arms and legs
- Areflexia
- Progression of symptoms over days to 4 weeks
- Relatively symmetric
- Mild sensory symptoms and signs
- Cranial nerve involvement, especially facial diplegia
- Recovery beginning 2–4 weeks after progression ceases
- Autonomic dysfunction
- Absence of fever at the outset

Electrophysiologic features*

- Reduction in motor conduction velocity
- Prolonged distal motor latencies
- Prolonged F-wave latency
- Partial motor conduction block or abnormal temporal dispersion

Laboratory features

- Elevated cerebrospinal fluid (CSF) protein after the first week of symptoms

*≥1 of 4 criteria in each of ≥2 nerves or ≥2 of 4 criteria in 1 nerve

1. Asbury AK, Cornblath DR. Ann Neurol. 1990;27(suppl):S21–24.
2. Hadden RDM *et al*. Ann Neurol. 1998;44(5):780–788.

GBS associated with Zika virus

- During the Zika virus outbreak in French Polynesia evidence emerged of GBS cases associated with Zika virus infection[1]
  - Of 42 patients with GBS, 100% had neutralising antibodies against Zika virus compared with 54 patients (56%) in the control group

- **Case study:[2]**
  - Patient presented with GBS seven days after experiencing flu-like symptoms
    - Usual etiologies were eliminated
    - Serological analyses indicated a recent infection with Zika virus

- Since the beginning of the current Zika epidemic, the incidence of GBS in French Polynesia has increased 20-fold[2]

- Not all individuals infected with the Zika virus will develop GBS[3]
  - Approximate risk is 1 in 4,000 infected patients[1]

1. Cao-Lormeau VM *et al*. Lancet. 2016;387(10027):1531–1539.
2. Oehler E *et al*. Euro Surveill. 2014;19(9).
3. Anaya JM *et al*. BMC Med. 2016;14:49.

Prevalence of GBS associated with Zika virus[1]

- An increased incidence of GBS cases and/or laboratory confirmation of a Zika infection among GBS cases has been reported in 16 countries and territories worldwide:

Classification	Country/Territory/Area
Reported increase in incidence of GBS cases, with at least one GBS case with confirmed Zika virus infection	• Brazil • Colombia • Dominican Republic • El Salvador • French Guiana • French Polynesia • Honduras • Jamaica • Martinique • Suriname • Venezuela (Bolivarian Republic of)
No increase in GBS incidence reported, but at least one GBS case with confirmed Zika virus infection	• French Guiana • Haiti • Martinique • Panama • Puerto Rico

1. World Health Organization. Zika situation report. Available at: http://apps.who.int/iris/bitstream/10665/249518/1/zikasitrep11Aug2016-eng.pdf?ua=1. Accessed August, 2016.

Zika-related GBS: French Polynesia

- Preliminary data from a French Polynesia report indicated that Zika-related GBS patients had the following characteristics:[1]
  - Rapid evolution of disease (median duration of 6 days from onset of neurological symptoms to nadir) and a median plateau phase of 4 days
  - Flaccid quadriparesis (74%), facial palsy (64%), and respiratory failure (29%)
  - Electrophysiological findings compatible with acute motor axonal neuropathy (AMAN) type (axonal polyneuropathy with normal sensory action potential)
- Findings from a case report in French Polynesia, suggest that the pathophysiological mechanism of Zika-related GBS could be immunological, due to genetic evolution of the virus to a more pathogenic genotype, or a susceptibility of this population[2]
- It is unclear if past infections with dengue virus (which has been associated with GBS) may be a pre-disposing factor for developing GBS during Zika virus infection[1,2]

1. Cao-Lormeau VM *et al*. Lancet. 2016:387(10027):1531–1539.
2. Oehler E *et al*. Euro Surveill. 2014:19(9).

Zika-related GBS: Columbia

- Subsequent observations from well documented cases in Columbia suggest Zika-related GBS cases represent the classical form with typical demyelinating features[1]
  - GBS followed typical symptoms of Zika infection with fever (69%), rash (59%), and headache (34%)
  - Average time between viral infection and onset of GBS was 4 days
    - Limb weakness (97%), paresthesias (76%), facial paralysis (50%)
    - ICU (59%), ventilated (31%), mortality (4%)
    - Biospecimens (serum, urine, CSF) indicated definite Zika infection in 41%, probable in 43%, and possible in 16%
    - EMG patterns:
      - AIDP (74%)
      - AMAN (6%)
      - Equivocal (11%)
      - Inexcitable (2%), AMSAN (2%), NL (4%)
  - Incidence of approximately 9 cases per 100,000 people in Columbia during outbreak

ICU: intensive care unit, EMG: electromyography, AIDP: acute inflammatory demyelinating polyneuropathy, AMAN: acute motor axonal neuropathy, AMSAN, acute motor sensory axonal neuropathy

1. Carlos Pardo-Villamizar (personal communication).

Zika-related GBS: Brazil

- Observed patterns included demyelinating and axonal forms of GBS[1]
  - Approximately 50–75% had typical AIDP, others with GBS variants or rarely myeloradiculitis (rates varied by region, e.g., Recife, Rio de Janeiro, São Paulo)
  - 88% had clinical evidence of preceding Zika infection
  - Some GBS cases occurred simultaneously with acute viral infection (possible acute infective neuritis)
    - Positive PCR for Zika in serum at time of onset of GBS
    - MRI with lumbosacral nerve root enhancement in some cases
  - Pain and paresthesias were prominent in approximately 50% of cases
  - Limb weakness (74%), ventilated (24%), mortality (7%)
  - Incidence of approximately 7 cases per 100,000 people in Brazil

PCR: polymerase chain reaction, MRI: magnetic resonance imaging

1. James Sejvar, M.D., Oswaldo Nascimento, M.D., Amilton Barreira, M.D. (personal communication).

Summary of treatment guidelines for GBS

The current guidelines recommend the following:

- **Indication**
  - Intravenous immunoglobulin (IVIg) therapy, administered within 2 weeks of symptom onset, is the appropriate treatment for GBS[1-3]
  - Plasma exchange (PE) can be used but IVIg is usually preferred due to its wide availability and safety profile[1-2]
    - IVIg manufacturing process has dedicated pathogen removal steps which deplete viruses from the product[4]
  - There are no data to suggest treatment responses vary with Zika-related GBS
- **Dose**
  - An IVIg dose of 2 g/kg over 5 days is suggested[1-3]
  - A second course can be given in case of relapse (treatment-related fluctuations)[3]

1. Patwa *et al*. Neurology. 2012;78(13):1009–1015.
2. Donofrio *et al*. Muscle Nerve. 2009;40(5):890–900.
3. Elovaara *et al*. Eur J Neurol. 2008;15(9):893–908.
4. PPTA. Zika Virus and Plasma Protein Therapies. Available at http://www.pptaglobal.org/media-and-information/ppta-statements/969-zika-virus-and-plasma-protein-therapies. Accessed June, 2016.

Summary

- Mosquito-borne Zika virus transmission has been reported in 69 countries
- Zika virus can be transmitted via:
  - The bite of infected species of the *Aedes* mosquito
  - Perinatal route
  - Sexual activity
  - Blood transfusion
- Zika virus infection has been associated with cases of congenital microcephaly and GBS
- Zika-related GBS presents as the typical demyelinating form and/or possibly the AMAN variant
  - Preceding infection within 7 days of onset of GBS
  - Median duration of 6 days from presentation of symptoms to nadir
- IVIg and PE are proven effective therapies for GBS; IVIg may be preferred due to its ease of administration and wide availability