NATIONAL SURVEILLANCE OF GUILLAIN-BARRE SYNDROME IN THE PHILIPPINES

NATIONAL GBS SURVEILLANCE TEAM:

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This study is being done in support of the Acute Flaccid Paralysis program of the Department of Health and World Health Organization, in cooperation with the Philippine Neurological Association and Child Neurology Society of the Philippines.

INTRODUCTION

For 13 years of being Polio-free country, the Philippines was identified as high risk for wild Polio virus importation since 2012. One of the reasons why the Philippines was regarded as such is due to low or non- reporting of cases from health facilities as evidenced by the low non-Polio AFP rate of 0.73 last 2013 and a very low rate of 0.15 from January 1-May 31, 2014.

Guillain-Barré Syndrome (GBS) is the most common cause of acute flaccid paralysis in childhood in the post-poliomyelitis eradication era (Sladky, 2004). Recent reports of GBS incidence have utilized the Acute flaccid paralysis surveillance program of the World Health Organization. AFP surveillance is an essential strategy of the Polio Eradication Initiative adopted by the WHO in 1998. This is the gold standard for detection of poliomyelitis cases. Finding and reporting children with AFP, transporting stool samples for analysis, isolating and identifying poliovirus in the laboratory and mapping the virus to determine the origin of the virus strain are the four steps of the AFP surveillance (WHO The Polio Eradication Initiative, 2010).

GBS is an acute peripheral neuropathy characterized by rapidly developing ascending motor paralysis with variable autonomic dysfunction and cranial nerve palsy. An estimated incidence of GBS is between 1.1-1.8/100,000/ year (McGrogan, 2009). A meta-analysis of studies on GBS incidence showed an increase by 20% for every 10-year increase in age, and the risk of GBS was higher for males than females (Sejvar, 2011).

Thepathogenesis of GBS remains to be established. Molecular mimicry and subsequent antibody cross reactivity between structural components of both pathogens and myelin sheath of peripheral nerves is the most plausible proposed hypothesis (Jasem, 2013).

SIGNIFICANCE OF THE STUDY

This will be the first nationwide prevalence and epidemiological study of GBS among Filipino patients. This study is being done to support the AFP surveillance in the country as we are approaching the end game program for polio eradication. Likewise, valuable information on the epidemiology of GBS widens the understanding of the changing patterns of the disease incidence following exposure to new potential provoking factors (Sejvar, 2011). Outcome measures of the disease in terms of mortality and morbidity can assist clinicians and policy-makers to direct attention toward modifiable risk factors of adverse disease outcomes. In the conduct of this study, the investigators will likewise extend support to the AFP program in the Philippines for Polio eradication in the world.

OBJECTIVES

General Objective: To conduct a nationwide surveillance of Guillain-Barré Syndrome in the Philippines.

Specific Objectives:

1. To increase the case detection rate for AFP and GBS among age groups 0-15 years
2. To establish the incidence of GBS in the Philippines from September 1, 2014 to August 31, 2015.
3. To determine epidemiological and clinical features of GBS in the Philippines

METHODOLOGY

Population:

All patients presenting with acute flaccid paralysis who will be initially seen or referred to all participating neurologists nationwide from September 2014 to September 2015 will be screened according to the Acute Flaccid Paralysis Surveillance System. One thousand GBS cases will be the estimated sample size based on the worldwide annual incidence of GBS and the projected Philippine population of 100 million by 2015. All diagnosed cases of Guillain-Barre syndrome using the diagnostic criteria of the Asbury and Cornblath will be included in the study.

Approval from the Institutional Review Board (IRB) panel from the institution of the primary investigator will be obtained. Written informed consent and assent to participate in the study will be acquired from all patients or their relatives.

Duration: 2014-2015

Design: Prospective multi-centered cohort study

Definition of Terms:

a. Acute Flaccid Paralysis (AFP): is a **syndrome** manifested as floppy paralysis. It is not a disease condition.
b. AFP case: any child under 15 years of age with acute onset of floppy paralysis, or a person of any age in whom poliomyelitis is suspected by a physician.
c. AFP cluster: defined as 2 or more AFP case reported from one barangay/municipality within a period of 4 weeks
d. AFP hot case: A child less than 5 years old with less than 3 doses of OPV and had fever at the onset of asymmetrical paralysis or any person of any age whose stool sample yields a positive L20B isolate regardless of genotype
e. Participating neurologists: Members of the Philippine Neurological Association (PNA) and

Child Neurology Society of the Philippines (CNSP)

f. Medical Research Council scale for muscle strength is graded on the following:

GRADE	DESCRIPTION
5	Muscle contracts normally against full resistance
4	Muscle strength is reduced but muscle contraction can still move joint against resistance
3	Muscle strength is further reduced such that the joint can be moved only against gravity with the
	examiner's resistance completely removed
2	Muscle can move only if the resistance of gravity is removed
1	Only a trace or flicker of movement is seen or felt in the muscle or fasciculations are observed in the
	Muscle
0	No movement is observed

Table 2: Medical Research Council Scale for muscle strength

g. Medical Research Council sum score on admission: the sum of MRC grades (ranging from 0-5) of six bilateral muscle groups/ pairs: upper arm abductors, elbow flexors, wrist extensors, hip flexors, knee extensors, and foot dorsiflexors.

AFP Surveillance Program (see Manual of Operations included in the kit)

A. Case Detection and Notification

The Disease Surveillance Officers (DSOs)/Disease Surveillance Coordinators (DSCs) should conduct daily active case finding in coordination with the participating neurologist in the institution or region. To ensure that all cases are detected, DSOs/DSCs should also review patient's records/logbooks of the health facility based on the following differential diagnoses: Poliomyelitis, Guillain-Barre syndrome, Myelitis (i.e. Transverse myelitis, Pott's disease), traumatic neuritis, and other disease as long as AFP is manifested. Reporting of all patients that satisfy the standard case definition within 24 hours after detection, regardless of the physician's diagnosis will be done online to the designated project coordinator. Zero reporting of cases will be required from participating neurologists on a weekly basis through email or short message service (SMS). Centralized reporting will be done by each participating neurologist to the designated project coordinator, who will likewise, coordinate with the reference laboratory and NEC designated polio officer for confirmation of receipt of stool specimen and accomplished CRF.

B. Case Investigation

1. Verify if the case satisfies the case definition for AFP. DSO/DSC will coordinate with the

partner neurologist on the neurologic findings of the reported AFP case.

2. Interview and examine the case
3. Collect additional information
4. Collect stool specimen for the AFP age group0-15.
5. Submit the completed AFP and GBS CIF. GBS CIF will be accomplished by the partner neurologist.
6. Conduct 60-day follow-up examination

C. Case confirmation

1. Stool Collection and Storage procedures
2. Specimen transport procedure
3. "Hot case" definition
4. What to do when an AFP "Hot case" is reported?

D. 60-Day Follow-up

A follow-up visit to an AFP case is important to determine the presence of residual paralysis. All AFP cases should be followed up on the 60th day from onset of paralysis. Priority should be given to AFP case that falls in any of the following: without stool samples, stool samples were collected beyond 14 days from paralysis onset, cases classified as polio-compatible, AFP hot case. For cases with inadequate stool specimen or cases classified as polio-compatible, a complete follow-up neurologic evaluation should be conducted by a physician or a trained health worker and coordinated with the designated neurologist in the region to determine if the neurologic deficits are highly suggestive/compatible with polio. The Hughes functional scoring for GBS *(see table 2)* will be used to assess the neurologic outcome of the patients. This will be done by the designated neurologist.

The patient may be declared "lost to follow-up" after three failed attempts to locate him or her within 90 days after paralysis onset. Death of the patient before the 60-day follow-up should be reported immediately to RESU and NEC.

E. Case classification

Expert Panel Classification: the main responsibility of the AFP/Polio Expert ReviewCommittee is to review and classify all the AFP cases reported and entered into the surveillance system. Complete medical records with relevant information and laboratory results should be provided especially for cases with inadequate stool specimen to facilitate case classification.

For cases diagnosed with GBS with electrophysiologic studies, the following case classification will be used: AIDP, AMAN, AMSAN and MFS.

Guillain-Barre Study (GBS)

Data collection

Data collection will be done using a standardized GBS case record form with the following details: demographic characteristics, antecedent events, vaccination records, treatment given, available laboratory tests (i.e. electrophysiologic tests, CSF studies and neuro-imaging) and outcome.The participating neurologist will be required to accomplish the GBS case record form. Inter-site standardization process will be maintained on each site through quality control procedures on data entry and data processing. Each site will use the same set of forms. Epi-Info Version will be utilized as data entry program. Batch forms will be submitted to the data manager responsible for range checks and other basic data- cleaning procedures.

Clinical Investigation for GBS cases

Weakness severity will be estimated by calculating the Medical Research Council (MRC) sum score, which is defined as the sum of MRC grades (ranging from 0-5) of six bilateral muscle groups/ pairs: upper arm abductors, elbow flexors, wrist extensors, hip flexors, knee extensors, and foot dorsiflexors. The range of MRC sum scores is from 0 (tetraplegia) to 60 (no paralysis) (Verma, 2013). MRC scale for muscle strength is graded on the following (see table 2): Grade 5 (Muscle contracts normally against full resistance), Grade 4 (Muscle strength is reduced but muscle contraction can still move joint against resistance), Grade 3 (Muscle strength is further reduced such that the joint can be moved only against gravity with the examiner's resistance completely removed), Grade 2 (Muscle can move only if the resistance of gravity is removed), Grade 1 (Only a trace or flicker of movement is seen or felt in the muscle or fasciculations are observed in the muscle), and Grade 0 (No movement is observed) (MRC, 1981).

Presence of autonomic dysfunction characterized with either one of the following: cardiac arrhythmias, fluctuations in rate and blood pressure, sweating abnormalities, pupillary abnormalities, gastrointestinal dysfunction and urinary retention will be recorded. Likewise, the presence of respiratory impairment and need for ventilatory support will be noted.

Functional outcome of enrolled patients will be graded according to Hughes functional grading scale on three settings: on admission, upon discharge and on follow-up check-up.

Table 3: Hughes Functional grading scale for GBS (From Hughes et al, Lancet 1978)

Score	Description
0	Healthy
1	Minor symptoms or signs, able to run
2	Able to walk 5m independently
3	Able to walk 5m with a walker or support
4	Bed- or Chair-bound

5	Requiring assisted ventilation
6	Death

Patients with electrophysiological testing, if available, will be classified according to GBS subtypes as follows: AIDP, AMAN, AMSAN, and MFS.

Table 4: Baseline Characteristics of Children with GBS

Parameters	N (%)
Mean age (years) ± SD	
Sex (M:F)	
Time to peak deficit (days) 1-5 days 6-10 days 11-15 days 16-20 days	
Mean time to peak deficit (days) ± SD	
Antecedent illness URTI Diarrhea Nonspecific viral illness	
Nutritional Status Number with mass <3rd percentile for age, (%) Mean Z score for wt (SD) Mean BMI (SD)	
Season* Rainy Summer	
Polio immunization status OPV IPV	
Recent Vaccination (6-8 weeks from onset of symptoms) Flu MMR HiB OPV IPV Rabies Hepatitis Vaccine Others	

Table 5: Clinical features of patients with GBS

Parameters	N (%)
Cranial nerve involvement	
Facial palsy	
Bulbar involvement	
Neck flexor weakness	
Autonomic dysfunction	
Ventilatory support	
MRC sum score on admission* 51-60 41-50 ≤ 30	
Mean MRC sum score on admission*	
Baseline Hughes motor scale (Admission) 0-2 3-6	
Hughes motor scale upon discharge 0-2 3-6	
Hughes motor scale on 60-day follow-up 0-2 3-6	
Electrophysiologic test Primary demyelinating, AIDP Axonal, AMAN AMSAN MFS	
CSF protein (mg/dl) ± SD	
Intervention IVIg Plasmapheresis Others	
Outcome No Residual Neurologic deficit With Residual Neurologic deficit Death	

MRC: Medical Research Council scale, IVIg: Intravenous immunoglobulin, CSF: cerebrospinal fluid (Verma, 2013)

Microbiologic studies

a. Sample Collection

Two (2) stool specimens from all AFP and GBS cases will be analyzed for polio and non polio enterovirus using the WHO algorithm for virus isolation at the RITM National Polio Laboratory as part of its routine laboratory operations. Specific instructions for collection, storage and transport

of stool specimens are detailed in Annex Appendix VIII.

b. **Sample Receipt and Accessioning**

All stool specimens received shall be included under AFP surveillance and each be assigned with a unique laboratory ID number.

ex: S14-001 I/II

wherein: S=stool

14= year

001=sequential ID number

I/II= stool number (first or second)

c. Virus Isolation

Stool specimens received will be subjected to virus isolation. Stool specimens will be chloroform treated to degrade bacterial contaminants and the supernatant will be inoculated in two (2) cell lines; RD-A and L20B. Inoculated tubes will be observed for 5 days, and if negative, a blind passage will be performed. If specimen is negative after a total of 10 days observation, the specimen will be reported as negative. If a tube showed positive CPE (cytopathic effect) within the 10-day observation time frame, the WHO algorithm will be followed. If the specimen is regarded as L20B positive, the specimen will be subjected to intratypic differentiation test using Real Time PCR technique. The detailed poliovirus isolation algorithm is showed in Appendix IX.

d. Data Management and Results Transmittal

All stool specimens received will be encoded and included in the AFP surveillance database and will be reported together with all non-GBS AFP specimens on a weekly basis.

Statistical analysis

The computed sample size will be based on the estimated annual incidence of GBS and the projected population of the Philippines by 2015. Descriptive analysis of the data will be done. Frequency analysis of the variables will be determined.

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Appendix: Composition of the Team

Research Study Team	Position	Task
Dr. Aida M. Salonga	Senior Surveillance Supervisor	• Leads the entire program activity. Takes direct responsibility for completion of a funded program and directing.
Dr. Enrique A. Tayag	Co-supervisor	• Provides knowledge, advice, and technical inputs in the development of the surveillance proposal. • Analyzes data with statistician
Dr. Maria Joyce U. Ducusin	Co-supervisor	• Provides knowledge, advice, and technical inputs in the development of the surveillance proposal. • Analyzes data with statistician
Dr. Amado Ona Tandoc	Co-supervisor	• Provides knowledge, advice, and technical inputs in the development of the surveillance proposal especially in the methodology. • Analyzes data with statistician
Dr. Nina G. Gloriani	Co-supervisor	• Provides knowledge, advice, and technical inputs in the development of the research proposal. • Analyzes data with statistician
Dr. Vito Roque, Jr.	Chief, Public Health Surveillance and Informatics Division, DOH-NEC	• Provide technical inputs in the development of the surveillance proposal and finalization of technical report
Romina Calalang, RN	Nurse II, Vaccine Preventable Disease Surveillance Officer, Public Health Surveillance and Informatics Division, DOH-NEC	• Provide AFP surveillance data analysis • Assist in the written report on the result, findings, action taken and recommendation of the activity • Facilitate workshops and advocacy meetings • Capacitate chosen hospital sites and hired surveillance staff in case detection, reporting investigation and filling out of AFP CIF and GBS report
Chazel Marie Crucillo, RN	Senior GBS Surveillance Coordinator	• Supervision of GBS surveillance assistants • Conduct hospital visits for active surveillance or retrospective records review for AFP and GBS surveillance for NCR and region 4A • Receive and validate GBS reported cases from other GBS surveillance assistants for Luzon, Visayas and Mindanao cluster • Submit referred AFP cases referred by Pediatric/Adult neurologists to Regional VPD surveillance coordinator of NCR

		• Consolidate all GBS cases reported by GBS surveillance assistants
Cherryl Cahibaybayan (Luzon Area)	GBS Surveillanceassistants	• (May) conduct hospital visits (sites to be determined based on silent DRUs identified from 2009-2013) for active surveillance or retrospective records review for AFP and GBS surveillance to assigned Regions as necessary • Coordinate with Regional VPD surveillance officers and disease surveillance coordinators of health facilities for AFP and GBS cases reported from his/her covered Regions • Refer AFP cases to Regional VPD surveillance officers
	Statistician	• Assists in the protocol development • Data management and analysis.
	Encoder	• Encode all the data that will be collected from the study which will be used for analysis.