Review of a possible cluster of cases of Guillain-Barré Syndrome

in Duleek, Co.Meath

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Executive Summary

A cluster investigation was undertaken in response to concerns about a possible link between the occurrence of Guillain Barré Syndrome (GBS) in persons who lived in the village of Duleek where three industrial/commercial plants are located.

This cluster investigation process involved:

- confirming cases of GBS that have occurred in the area
- determining whether the number of cases was greater than the number expected to occur by random chance
- obtaining detailed information on each case including any possible exposures in the time period before onset of GBS symptoms

Summary of Findings:

1. Three persons with GBS were identified as having lived in Duleek with a time of disease onset between 2010 and 2014. Allowing for the wide variation in small expected numbers this is in keeping with the expected incidence of the disease for this time period. The overall incidence for this disease in the Northeast is as expected.
2. Each person gave a history of preceding infection shortly before onset of their symptoms of GBS indicating a possible infectious disease cause.
3. No evidence of any environmental issue having a causal association with GBS was found.
4. The Environmental Protection Agency (EPA) and Meath County Council confirmed that the processes in place conform to best practice at the three commercial operations adjacent to the village and that there was no evidence of any non-compliance with these processes.
5. No common causal link was found between the three cases.
6. The most likely explanation for each individual case is a preceding infectious illness.
7. Random variation would account for the small group of cases who resided in the Duleek area.
8. A number of recommendations have been made relating to assessing any alleged risk to the health of the public and in regard to the issue of environmental stressors.

Introduction

In January 2015, two environmental health special interest groups (The Louth Meath Health Protection Group and Drogheda Environmental Group) contacted the Department of Public Health HSE-North East and requested that the HSE review a possible cluster of cases of Guillain-Barré Syndrome in the village of Duleek, Co Meath. They also raised concerns about the presence of an incinerator and a cement works in the village and their potential association with Guillain-Barré Syndrome.

In response the Department of Public Health convened a review team and conducted a cluster investigation in accordance with guidelines ("Guidelines for Investigating Clusters of Health Events" CDC, 2015).

Cluster

As used in the guidelines the term "cluster" is "an unusual aggregation, real or perceived, of health events that are grouped together in time and space and that are reported to a health agency"

Outline of Investigation

The steps involved in this disease cluster investigation were:

1. Establish a case definition
2. Confirm the suspected cases
3. Define the population in which the cluster occurred and the time period involved, search for additional cases within that population, and draw conclusions about the "unusualness" of the cases
4. Review the literature for risk factors and exposure hypotheses
5. Perform an exposure assessment
6. Generate biologically plausible hypotheses.

For membership of the review team, see Appendix 1.

Background

Case Definition

Establishing a case definition was important to ensure that the cluster investigation studied only the relevant disease in the relevant population and appropriate time period. The case definition agreed for the review is as follows, "*a clinically confirmed case of GBS diagnosed since 2010 in a person resident in Duleek at disease onset*".

Confirmation of cases

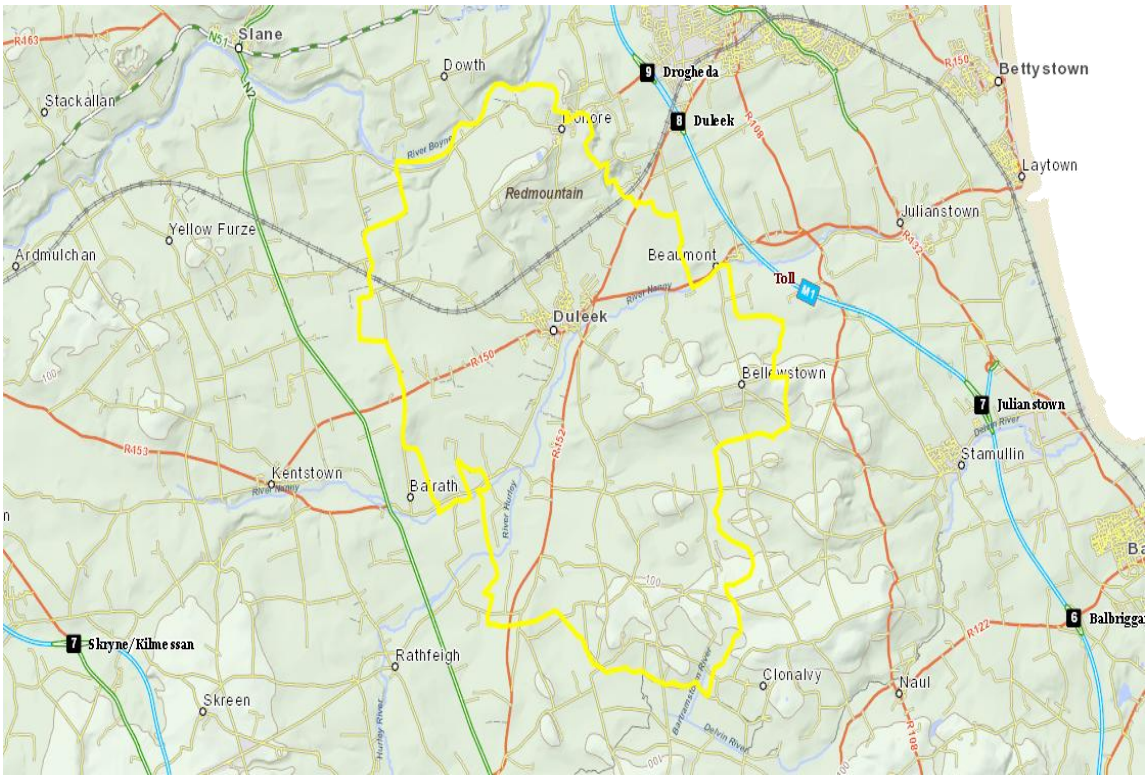
Six possible cases were brought to the attention of the review group at the initial meeting with the key informants. All six were interviewed by a public health physician and medical records were examined to ascertain if they had a clinically confirmed diagnosis of GBS and if they had been resident in Duleek at the time of disease onset. Patients who had alternate diagnoses or who were not resident in Duleek when diagnosed with GBS did not meet the case definition and therefore were excluded from the review. Only three cases were verified to meet the case definition.

Check for further cases

The Hospital In-Patient Enquiry (HIPE) system records were examined to identify all GBS admissions from Co. Meath since 2010. GBS case dates of admission were then used to check both hospital records and national registers. No further cases of GBS were revealed among Duleek residents during the relevant time period.

Description of Population in Duleek

All three confirmed cases live within the Duleek Primary Care Team (PCT) area (Map 1). The population of Duleek PCT is 7,088 (3,592 males; 3,496 females, Male : Female ratio 1 : 1.03)



Map 1: Map of the Duleek area with Duleek PCT highlighted in yellow

The census (2011) shows that the age profile of the population in Duleek is younger than the national age profile (CSO, 2015). In addition the population of Duleek PCT is more disadvantaged than the country as a whole and has a higher rate of unemployment. However fewer people in Duleek report their health as bad or very bad and there are less people in Duleek who report living with a disability compared to the national figures.

Within a 3.5 kilometre radius of the main street of the village there are three large scale commercial operations and a local waste water treatment site. Two industrial plants are located north northeast of the village; a cement works at Platin and an adjacent incinerator operated by Indaver. South of the village is an abattoir run by Eurofarms at Cooksgrove and southwest of the village there is a local sewage treatment facility at Mount Hanover.

Literature Review

Guillain Barré Syndrome (GBS) is characterised by acute onset of areflexic paralysis and was first described by Landry in 1859 and later named after two French neurologists in 1916. Since the virtual elimination of poliomyelitis, it now constitutes the commonest form of acute flaccid paralysis worldwide.

GBS is considered to be a group of peripheral nerve disorders differentiated by the distribution of the weakness in the limbs or the muscles innervated by the cranial nerves. The distribution of the different subtypes varies in different regions of the world.

Epidemiology

The incidence of GBS ranges from 0.89-1.89 cases per 100,000 person years and increases with increasing age. The number of cases is higher in males with a male to female ratio of 1.78:1 (Sejvar *et al*., 2011)

Two thirds of cases have an identified preceding infectious illness principally a diarrhoeal or respiratory illness typically three days to six weeks before symptom onset (Yuki & Hartung, 2012). There is evidence of a seasonal variation in the preceding illness with respiratory illness being more commonly associated with winter onset of GBS and gastrointestinal more commonly identified as the preceding illness in those with summer onset of GBS (Brian *et al*., 2013).

The most commonly identified preceding infection is that of campylobacteriosis with one meta-analysis identifying *Campylobacter jejuni* as the antecedent agent of infection in 30% of cases. (Poropatich *et al*., 2010). Cytomegalovirus has been identified as the precedent in about 10% of cases (Hadden *et al*., 2001; Jacobs *et al*., 1998). Epstein barr virus, influenza, mycoplasma and Hepatitis E have also been identified as preceding infections (Tam *et al*., 2007; Santos *et al*., 2013).

GBS is believed to be caused by an autoimmune attack on peripheral nerves, which can occur in previously healthy patients without any signs of other autoimmune diseases. Some of the infections most commonly identified as triggers of GBS (e.g. *Campylobacter jejuni*) are known to share structural similarities with components of peripheral nerves. Many different immunological abnormalities have been described in GBS, including antibodies directed against tissues in the nervous system and T cell and macrophage infiltration of nerves (Pritchard, 2010).

Clinical Course

In the majority of patients the illness continues to progress for one to three weeks after symptom onset (Hiraga *et al*., 2003). Two thirds of patients are unable to walk at the point when their symptoms are at their worst (Hughes *et al*., 2007). Respiratory insufficiency develops in 25% of patients and significant complications (pneumonia, sepsis, pulmonary sepsis, gastrointestinal haemorrhage) occur in 60% of patients who require ventilation (Hughes *et al*., 2005). For those patients most severely affected, 20% are unable to walk six months after the onset of their illness (Yuki & Hartung, 2012). In most patients their illness consists of a single episode of illness but in 7% of patients two or more episodes can occur with the mean interval between episodes being seven years (Kuitwaard *et al*., 2009).

Biological plausibility

The scientific evidence points to an infective trigger for GBS, there is no evidence in the literature to support a causal association between any environmental issue and GBS. Amongst the known infective triggers, campylobacter is the one most commonly identified, but viruses such as influenza and Epstein Barr can also act as triggers. The infective agent activates an auto-immune response in susceptible individuals probably due to cross reaction to antigens in the infective agent and in the neurological system.

Review of medical records and patient interviews

Methods

Consistent with Morbidity and Mortality Weekly Report (MMWR) Centre for Disease Control and Prevention (CDC) "Guidelines for Investigating Clusters of Health Events" (CDC, 2015), the case histories of identified cases were investigated through review of relevant medical records and face-to-face interviews. Written informed consent was obtained from the cases or their next of kin to examine their medical records. Review of medical records took place between 25/05/2015 and 30/06/2015. Two Public Health physicians from the Department of Public Health reviewed the cases' medical records at the treating hospitals. Medical records were reviewed using chart review templates that were developed for this cluster investigation by the Cluster Investigation Group (see Appendix 3). Two Public Health Physicians subsequently carried out interviews with the identified cases to collect further information and verify the diagnosis. Interviews of cases took place between 17/07/2015 and 21/07/2015 and were conducted using a standard questionnaire that was developed for this cluster investigation by the Cluster Investigation Group (see Appendix 4).

Results of chart review and interviews

All three cases presented to the Emergency Department of an acute hospital and were admitted at the time of presentation. All three cases fulfilled diagnostic criteria for Guillain Barré Syndrome and all had a diagnosis of Guillain Barré Syndrome confirmed by a consultant neurologist during admission.

The following main points were of relevance from interviews conducted with patients:

- All cases were on the mains public water supply (with which no significant issues were identified during the study period, see Section on Local Environment)
- All cases had either a preceding respiratory or diarrhoeal illness in the 2 months prior to onset of GBS
- None of the cases received influenza vaccination
- None of the cases were in direct contact with farm animals/livestock
- None of the cases had a history of significant travel

Background levels of GBS

Data on hospital discharges for GBS were extracted from the Hospital In-Patient Enquiry (HIPE) scheme to provide information on background levels of GBS. HIPE is a health information system designed to collect clinical and administrative data from patients in acute hospitals in Ireland. It is the principal source of national data on discharges from acute hospitals. The Healthcare Pricing Office (HPO) oversees the administration and management of this data source.

All data within HIPE is coded in a standardised way using strict rules and definitions to ensure that the data is comparable between hospitals. These rules and definitions are contained within a data dictionary freely available online at http://www.hpo.ie/HIPE_Data_Dictionary.htm HIPE uses a clinical coding system to assign the diagnoses of patients discharged from hospital in a standardised way. The first diagnosis in HIPE is known as the principal diagnosis and reflects the main reason the patient was admitted to hospital. Up to 30 diagnoses can be recorded within the HIPE system, with diagnoses 2-30 indicating other diseases or conditions that the patient had. All discharges recorded in HIPE between 1st January 2005 and the 31st of December 2014, were coded using the ICD 10AM clinical coding system. In this system, Guillain Barré Syndrome is assigned the code G61.0. When looking at where a patient lives, the county of residence is the lowest level at which a patient's address is recorded in the national HIPE system.

From the HIPE system, all patients discharged with a principal diagnosis of GBS between the years 2005 and 2014 were extracted. In keeping with the findings from the literature, Figure 1 shows that during the study period, the number of patients discharged nationally increases with age and is higher in males than females (see also table in Appendix 2).

The number of patients discharged by year for Ireland and the North East are presented in Fig. 2. Discharges for patients resident in the North East, range from 0 to 13 over the 10 year period from 2005 to 2014. Comparison of hospital activity data and incidence rates by county for the North East and Ireland demonstrates variation across years with no underlying trend in the data. This is not unexpected with rare diseases.

Figure 1: Number of patients discharged nationally with GBS by age and gender (2010 – 2014). Data were extracted from HIPE with the following conditions: Principal Diagnosis = G610, Admission Type = emergency, restricted to inpatients, one episode per patient, residence code restricted to 26 counties of the Republic of Ireland.

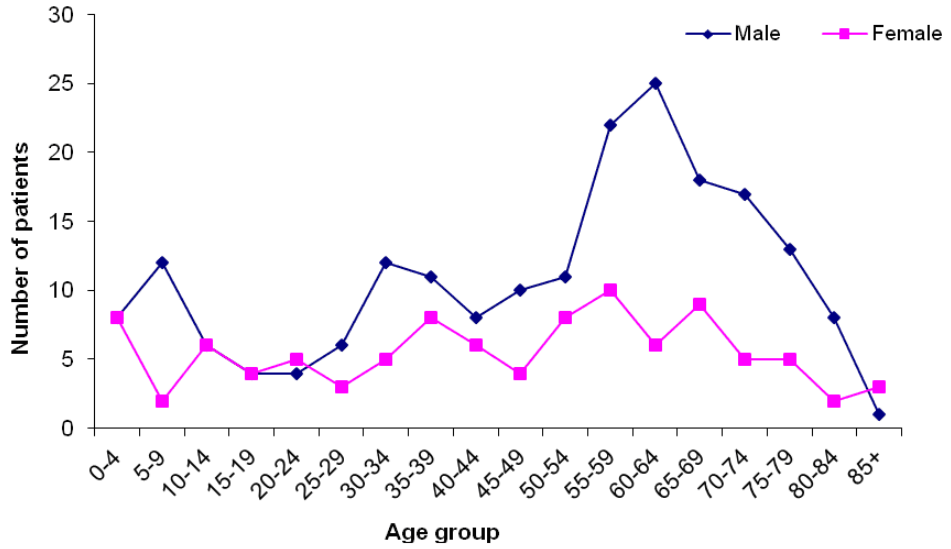
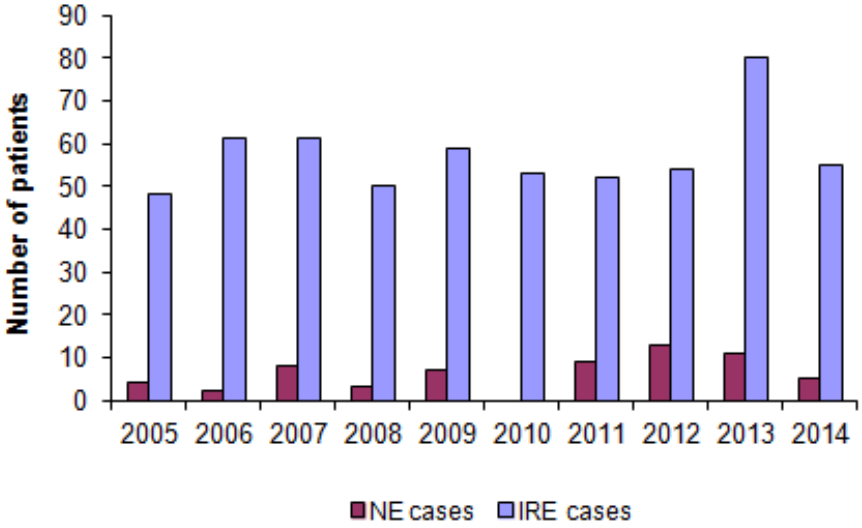


Figure 2: Number of patients discharged with GBS by year (2005 – 2014). IRE: total patients discharged for Ireland, NE: total patients with north east address. Data were extracted from HIPE with the following conditions: Principal Diagnosis = G610, Admission Type = emergency, restricted to inpatients, one episode per patient, residence code restricted to 26 counties of the Republic of Ireland.



Background levels of preceding infective illnesses

The epidemiology of two of the common preceding illnesses was examined. This was based on notification data. As with most notifiable infectious there is a degree of under-reporting.

Epidemiology of Campylobacter

Campylobacteriosis is a common, generally self limiting, gastrointestinal illness caused by a gram negative bacterium of the genus Campylobacter. Infection with Campylobacter is characterised by diarrhoea, cramps, fever and abdominal pain and the most common route of transmission is faecal-oral through ingestion of contaminated food or water. Handling or eating of undercooked or raw poultry has been shown to be particularly high risk for the transmission of Campylobacter (FSAI, 2015). Campylobacteriosis is the commonest notified cause of gastrointestinal illness in Ireland and Europe.

National and regional cases of campylobacter notified and crude incidence rates between 2010 and 2014 are outlined in Table 1.

- In 2010 there were 1660 cases of campylobacter notified corresponding to a national crude incidence rate of 36.2 per 100,000 population. The rate for the north east (Cavan, Louth, Meath and Monaghan) and specifically County Meath was lower at 24.3 and 18.5 per 100,000 population respectively.
- In 2011, there were 2427 cases of campylobacter notified corresponding to a national crude incidence rate of 52.9 per 100,000 population. The rate for the north east and specifically County Meath was lower at 44 and 33.7 per 100,000 population respectively.
- In 2012, there were 2388 cases of campylobacter notified corresponding to a national crude incidence rate of 52 per 100,000 population. The rate for the north east and specifically County Meath was lower at 45.4 and 33.7 per 100,000 population respectively.
- In 2013, there were 2,275 cases notified nationally which corresponds to a crude incidence rate for Ireland of 49.6 per 100,000 population. In the north east for the same year, the crude incidence rate was lower than the national at 35.5 cases per 100,000 population. The crude incidence rate for County Meath in 2013 was approximately half the national rate with 20.1 cases notified per 100,000 population.
- Preliminary figures for 2014 demonstrate that there were 2617 cases of campylobacter notified with 194 notified from the north east. This corresponds to a crude incident rate of 57 per 100,000 population for Ireland and 44 per 100,000 population for the north east.

- Between 2010 and 2014 there were 30 outbreaks of campylobacter reported nationally but no outbreaks were associated with the North East (including County Meath) during this timeframe.

Table 1: Number of Campylobacter cases notified (n) and Crude Incidence Rate/100,000 population (CIR). All data were extracted from the Computerised Infectious Disease Reporting System maintained by the Health Protection Surveillance Centre (HPSC) and Departments of Public Health

Campylobacter	2010 n (CIR)	2011 n (CIR)	2012 n (CIR)	2013 n (CIR)	2014 n (CIR)
Co. Meath	34 (18.5)	62 (33.7)	62 (33.7)	37 (20.1)	69 (37.5)
North East	107 (24.3)	194 (44.0)	200 (45.4)	155 (35.2)	194 (44.0)
Ireland	1660 (36.2)	2427 (52.9)	2388 (52.0)	2276 (49.6)	2617 (57.0)

Epidemiology of Influenza

Influenza is a common respiratory illness caused by an RNA virus of which there are three types: Influenza A, B and C. Influenza A and B viruses are primarily responsible for all human infections and are mainly transmitted by coughing and sneezing. The virus circulates in the population through localised outbreaks, annual epidemics and less frequently, global pandemics. Common symptoms include fever, nausea, sore throat, cough, muscle pain, weakness and fatigue, however, infection in vulnerable populations, e.g. the elderly, often leads to pneumonia and death. A seasonal influenza peak is generally seen in the winter months. The success of the virus lies in its ability to undergo mutations that allow the evolution of new or adapted viral strains to which natural immunity in the human population is low. This ability to evolve has lead to a number of global influenza pandemics, including the most recent H1N1 virus pandemic in 2009/2010 which was characterised by infection and high mortality rates in younger age groups.

A number of surveillance systems collect information nationally and regionally on Influenza (HPSC, 2015). These systems include the Sentinel GP network and Out of Hours GP service which provide details on influenza like illness (ILI) circulating in the community, the National Virus Reference Laboratory which analyses and genetically types strains of influenza, the Hospital surveillance system that collects data on ILI and influenza in hospitalised patients and the national notification system which collects data on both clinically and laboratory notified cases of the virus. Together, these surveillance systems provide an accurate and timely overview of the transmission of influenza virus in Ireland and aim to provide an early warning of the circulation of the virus in the population. A national overview of each influenza season from 2010 is outlined:

- During 2010/2011 season, following the Influenza A (H1N1) pandemic in the 2009/2010 season, influenza activity peaked during the first week of 2011 with 202.1 sentinel GP ILI consultations per 100,000 population. Influenza A (H1N1) was the predominant virus with influenza B occurring later in the season. There were 2233 influenza cases notified during this timeframe of which 945 cases were hospitalised. There were 38 influenza associated deaths during the 2010/2011 season.
- During 2011/2012 season, influenza activity peaked in February 2012 with 41.3 sentinel GP ILI consultations per 100,000 population. Influenza A(H3) was the predominant influenza virus circulating during this time frame with a very small proportion of influenza B also detected. There were 600 influenza notifications reported with 147 cases hospitalised during this period. There were 13 influenza associated deaths during the 2011/2012 season.
- During 2012/2013 season, influenza activity peaked in the first week of January 2013 with 59.3 sentinel GP ILI consultations per 100,000 population. A second peak was also seen five weeks later with a rate of 59.1 per 100,000 population. This constituted a prolonged period of influenza activity which lasted for 14 weeks in total. Influenza B was the main virus circulating between January and February 2013, followed by influenza A(H3) and A(H1N1) for the reminder of the season. There were 1619 cases of influenza notified during this timeframe with 471 cases hospitalised. There were 32 influenza associated deaths reported during the 2012/2013 season.
- During 2013/2014, influenza activity occurred during late February/early March 2014 with an influenza peak of 54.5 sentinel GP ILI consultations per 100,000 population (HPSC, 2013). Influenza A (H3) was the most common virus circulating along with the pandemic influenza A strain (H1N1). There were 693 confirmed influenza cases hospitalised during the 2013/2014 influenza season. Of the 1718 influenza cases notified, influenza was reported as a cause of death in 43 cases during this period.
- Preliminary data for the 2014/2015 season demonstrated a similar broad distribution of influenza between February and March of 2015 (HPSC, 2015). The most common strains were again influenza A (H3) and A(H1N1) with also influenza B circulating. There were 981 patients hospitalised with influenza and 41 influenza associated deaths.

Epidemiology of other preceding infections

Other possible infectious antecedents (mycoplasma, Epstein Barr, Hepatitis E and cytomegalovirus) are less common and were not notifiable during the study period.

Local Environment

Large Scale Commercial Operations

There are three large scale commercial operations in the vicinity of Duleek village; an incinerator operated by Indaver Ireland, an adjacent cement works operated by Irish Cement and an abattoir located to the south of the village. The village is also served by a waste water treatment plant at Mount Hanover.

The incinerator operated by Indaver Ireland commenced construction in September 2008. Waste activities started under licence from the EPA at the site on the 15th of August 2011. This date is after the date of diagnosis of the first case in 2010. Indaver applied for a review of the licence in 2012 seeking to increase the capacity of the facility to 235,000 tonnes per annum and to allow for the incineration of hazardous waste. To facilitate this further increase in capacity, Indaver also applied to extend the waste acceptance and dispatch hours. This licence review was granted in June 2015.

The facility operated by Irish Cement at Platin was first licensed by the EPA in January 1996 but has been in existence at that site since 1972. On the site there is a quarry from which the bulk of the raw materials are extracted and the cement production plant. There are two operational kilns in the cement production plant.

The abattoir at Cooksgrove trading as Euro Farm Food is licensed to process no more than 300 cattle per day. It operates between 7am and 7.30pm though there is traffic to and from the site outside of these hours. There are a number of waste materials generated at the site including lairage slurry, paunch and treated effluent which are disposed of offsite by means of landspreading in accordance with a nutrient management plan.

A new waste water treatment plant at Duleek was developed in 2009 to respond to the increased population in the area. The new plant has an increased capacity of 7,000 population equivalent per year and serves the population in Duleek and surrounds.

Biosolid use on Agricultural Land

The spreading of biosolids on agricultural land is carried out in accordance with the Meath County Council Protocol for the Use of Biosolids in Agriculture in County Meath . Under this protocol only treated wastewater treatment sludges may be applied to agricultural lands in a way which does not harm humans, animals or the environment. The protocol specifies on which land the sludge may be spread and the conditions that must be adhered to. The treatment processes, required to render

the sludge biologically inactive, are specified within the protocol. In addition, permission to spread must be obtained from the council prior to any spreading. Spreading periods are defined in the Good Agricultural Practice Regulations 2014. Under these, the spreading of chemical fertiliser and organic fertiliser (other than farm manure) is prohibited between 15th of October and 15th of January. Spreading of farmyard manure is prohibited between 1st of November and the 15th of January.

Land owners may also enter into private arrangements for the spreading of other forms of biosolid waste on their own land once strict criteria are met and documented for inspection by either the County Council or Department of Agriculture inspectors. These processes must also adhere to the prohibition periods defined in the Good Agricultural Practice Regulations 2014.

No spreading under this protocol took place in the time period before symptom onset in any of the three cases in the Duleek area.

Spreading of waste by products from the Abattoir at Cooksgrove is under a Nutrient Management Plan agreed with the EPA.

Public Water Supply

There were no microbiological issues with the public water supply in the area of Duleek over the period covered by this study (2010 – 2014). Furthermore, there were no significant exceedences with public health implications found upon testing of the public water supply for chemicals and pesticides during the same time period. Details on water sampling can be obtained from Meath County Council (http://www.meath.ie/)

Conclusions

1. The number of GBS patients in the Duleek area, during the time period investigated is in keeping with the expected incidence of the disease for this time period allowing for the wide variation in small numbers when the incidence of rare diseases is examined.
2. Each person gave a history of preceding infection shortly before the onset of their symptoms of GBS
3. No evidence of any environmental issue having a causal association with GBS was found.
4. EPA and Meath County Council confirmed that best possible processes were in place at the three commercial operations adjacent to the village and that there was no evidence of any non-compliance with these processes

Recommendations

1. A national Environment and Health Unit should be formed to assess alleged risks to public health from environmental stressors
2. This unit should put a surveillance system in place to monitor health data and assess any unusual incidents of disease or syndromes in the population
3. As there is currently no national register for rare diseases including GBS, consideration should be given to establishing such a register as per the recommendation in the National Rare Disease Plan for Ireland 2014-2018 (DOH, 2014) for an All-Ireland Network of Rare Disease Registries.

References

Brian S, Webb A, Zentar M, and Turner MR. (2013) Seasonal variation, sub-type and prodromal illness in Guillain-Barré Syndrome. Journal of Neurology, Neurosurgery and Psychiatry, 38:196

CDC, 2015. MMWR CDC Guidelines for Investigating Clusters of Health Events. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/00001797.htm

CSO, 2015. Census 2011 data available at: http://www.cso.ie/en/census/census2011reports/

DOH, 2014. National Rare Disease Plan for Ireland 2014-2018, Department of Health 2014. Available at: http://health.gov.ie/blog/publications/national-rare-disease-plan-for-ireland-2014-2018/

FSAI (2005). FSAI Advises on Need to Control Campylobacter Contamination in Poultry. Available at: https://www.fsai.ie/news_centre/press_releases/campylobacter_EFSA_28012015.html

Hadden RDM, Karch H, Hartung HP, et al. (2001) Preceding infections, immune factors, and outcome in Guillain-Barré syndrome. Neurology; 56:758-65,

Hiraga A, Mori M, Ogawara K, Hattori T, Kuwabara S. (2003) Differences in patterns of progression in demyelinating and axonal Guillain-Barré syndromes. Neurology; 61:471-4

HPSC (2013). Annual Epidemiological Report 2013, Available at: http://www.hpsc.ie/AboutHPSC/AnnualReports/File,15139,en.pdf

HPSC (2015). Influenza surveillance in Ireland during the 2014/2015 season (slideshow). Available at: http://www.hpsc.ie/A-Z/Respiratory/Influenza/SeasonalInfluenza/Surveillance/InfluenzaSurveillanceReports/2014201515Season/File,15201,en.pdf

HPSC (2015). Influenza surveillance reports. Available at: http://www.hpsc.ie/A-Z/Respiratory/Influenza/SeasonalInfluenza/Surveillance/InfluenzaSurveillanceReports/

Hughes RAC, Swan AV, Raphaël JC, Annane D, van Koningsveld R, van Doorn PA. (2007) Immunotherapy for Guillain-Barré syndrome: a systematic review. Brain; 130:2245-57

Hughes RAC, Wijdicks EF, Benson E, et al. (2005) Supportive care for patients with Guillain-Barré syndrome. Arch Neurol; 62:1194-8

Jacobs BC, Rothbarth PH, van der Meché FGA, et al. (1998) The spectrum of antecedent infections in Guillain-Barré syndrome: a case-control study. Neurology; 51:1110-5

Kuitwaard K, van Koningsveld R, Ruts L, Jacobs BC, van Doorn PA. (2009) Recurrent Guillain-Barré syndrome. J Neurol Neurosurg Psychiatry; 80:56-9

Poropatich KO, Walker CL, Black RE. (2010) Quantifying the association between Campylobacter infection and Guillain-Barré syndrome: a systematic review. J Health Popul Nutr, 28:545-52.

Pritchard J, (2010) Guillain Barré Syndrome. Clinical Medicine *Vol 1*0, No 4: 399–401

Santos, L., Mesquita, JR, Rocha Pereira, N, Lima-Alves,C, Serrão,R, Figueiredo, P, Reis, J, Simões, J, Nascimento, MS, Sarmento A, (2013) Acute Hepatitis E Complicated By Guillain-Barré Syndrome In Portugal, December 2012 – A Case Report. Eurosurveillance, Volume 18, Issue 34

Sejvar JJ, Baughman AL, Wise M, Morgan OW. (2011) Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis. Neuroepidemiology, 36:123-33

Tam CC, O'Brien SJ, Petersen I, Islam A, Hayward A, Rodrigues LC (2007) Guillain Barré Syndrome and Preceding Infection with Campylobacter, Influenza and Epstein Barr Virus in the General Practice Research Database. PLoS ONE, 2(4): e344. doi:10.1371/journal.pone.0000344

Yuki N and Hartung HP (2012) Guillain Barré Syndrome. New England Journal of Medicine, 366;24: 2294-2304

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Dr. Ina Kelly/Environmental Public Health Group

Ms. Aishling Sheridan, Research Officer, HSE North East

Neurological expertise was provided by Dr Sean Connolly, Consultant in clinical neurophysiology, St Vincent's University Hospital Elm Park.

HSE Clinical Library Services

The Louth / Meath Health Protection Group

Drogheda Environmental Group

Appendix 1: Membership of the Investigation Group

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Dr. Peter Finnegan, Consultant in Public Health Medicine. HSE-North East

Dr. Howard Johnson, Consultant in Public Health Medicine. Health Intelligence Unit. HSE

Dr. Declan Mc Keown, Consultant in Public Health Medicine. Health Intelligence Unit. HSE

Dr. Elaine Brabazon, Ph.D., Surveillance Scientist. HSE-North East

Dr. Elyce McGovern, Specialist Registrar Public Health Medicine. Health intelligence Unit. HSE

Dr Chantal Migone, Specialist Registrar Public Health Medicine. HSE-East

Appendix 2: Number of patients with principal diagnosis of GBS by five year age group and gender (2010 – 2014)

No pts	Male	Female
0-4	8	8
5-9	12	2
10-14	6	6
15-19	4	4
20-24	4	5
25-29	6	3
30-34	12	5
35-39	11	8
40-44	8	6
45-49	10	4
50-54	11	8
55-59	22	10
60-64	25	6
65-69	18	9
70-74	17	5
75-79	13	5
80-84	8	2
85+	1	3
Total	196	99

Appendix 3: Chart review template developed for this cluster investigation by the Cluster Investigation Group

Demographics	MRN
	Name
	DOB
	Address
	Gender
	Address* at symptom onset
	Length of time at address
	GP
Hospital Admission	Date of first hospital admission
	Hospital admitted to
	LOS
	Principal consultant
Clinical Presentation	Date of first presentation
	Date of symptom onset (approx)
	LRTI / Diarrhoea
	Date & duration of prodromal illness
	Preceding Surgery
	Date & location of surgery
Symptoms	Weakness
	Progressing over 4/52
	Ascending/ descending progressive symmetrical >1 limb
	Facial weakness
	Dysphasia
	Dysarthria
	Swallow problems
	Ascending sensory loss
	Paraesthesia
	Sweating altered
	Urinary hesitancy
	Ocular symptoms
	Back pain
	Sensory symptoms
	Monophasic course from onset to worst symptoms

Signs	Hyporeflexia
	Intact reflexes
	Hypereflexia
	Hypotonia
	Ataxia
	Reduced sensation
	Respiratory muscle paralysis/failure
	Facial weakness
	Fluctuation of HR, Temp, BP
	Bulbar weakness
	Paralytic ileus
	Bilateral and flaccid weakness of limbs
Underlying pathology	
Vaccination history	
Absence of alternative diagnosis	
Investigations & results	Lumbar Puncture 1
	Protein level
	WCC
	Lumbar Puncture 2
	Protein level
	WCC
	Nerve Conduction Studies
	Electrolytes IADH
	Antibody screen
	Spirometry
	ECG
	Microbiology
	Others
Diagnostician (GBS)	
Neurology consultant opinion	
Date of confirmed GBS diagnosis	
Treatment received	Ventilation
	Plasma exchange
	IVIg +/- PLEX
	Other
	Steroid
ICU admission	
Date of discharge from hospital	
Symptomatic on discharge	
Follow Up	Rehabilitation admission
	Dates and details of subsequent hospitalisations
	Long term sequelae
	Awareness of any other cases

** information may not be available in chart*

Appendix 4: Interviews were conducted based on a standard questionnaire that was developed for this cluster investigation by the Cluster Investigation Group

Interview Questionnaire GBS: List of topics covered

Patient No.

Confirm address at time of symptom onset

Mark address on map

Antecedent time (2 months prior to onset)

Timeframe illnesses/ antecedent events date of onset

Respiratory

Diarrhoeal

Vomiting / Nausea

If any illness:

?Seek medical attention

?See GP/See hospital consultant

?Any samples sent

Flu vaccine history

Surgeries Type / Hospital / Consultant

Trauma

Were any family members ill prior to you becoming unwell?

Water supply

Well

Group water scheme

Problems with the supply

Activities

Farming / walking through farmland

Exposure to animals

Pets

Livestock

Swimming

Travel hx in 3 months prior to onset

Camping / Hillwalking / walking through farmland

What activities were you involved in regularly prior to your illness?

Is there any family history of illness?

Can you think of anything that might have triggered your GBS?

How did this illness impact on your life?

How are you now?

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

Appendix 5: Template Patient Information letter

Department of Public Health

Review of cases of Guillain Barré Syndrome

Dear

Thank you for taking my phone call previously. As discussed, the Health Service Executive (HSE) is now conducting a review of cases of Guillain Barré Syndrome (GBS) diagnosed since (timeframe) in the area. A committee, led the Director of Public Health, and drawing on relevant experts, will work to examine the cases of all patients who have developed **confirmed** GBS.

In order to thoroughly investigate this issue, the investigators will need to gather as much information as possible about patients who have had or have GBS. To assist us in this work, we are asking that you give your consent to allow your medical records to be included in the review. This will involve examination of your hospital and general practice (GP) records by doctors in public health .They will ensure the medical confidentiality of these is protected, just the same as it would be with your doctor or in hospital.

It is very important that all patients diagnosed with GBS in the area participate in the review, so that a complete investigation can be made. If however you choose not to participate in the review, this will not affect your health care or the management of your condition in any way.

I would be grateful if you could reply to this request, using the enclosed card, indicating whether or not you agree to participate in the review**.** The card should be sent to Department of Public Health, using the enclosed stamped envelope.

If you wish to discuss the review further with one of the doctors involved, you can phone the Department of Public Health on the enclosed number.

I hope you will be able to assist the HSE in this review,

With every good wish,

Yours sincerely

_____

Director of Public Health

Appendix 6: Template Consent Form

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

Department of Public Health

Consent Form for Participation in the review of cases of Guillain Barré Syndrome

*Please tick **one** of the boxes below*

I have read the information letter provided and agree to participate in the review of Guillain Barré Syndrome ☐

I have read the information letter provided and do not want to participate in the review of Guillain Barré Syndrome. ☐

Signature: _____
Date: _____
Name: _____
Address: _____
_____
_____
DOB: _____

If you agree to participate in the review, please provide the name of your GP and the name of the consultant and the hospital where you were diagnosed with GBS. If more than one hospital was involved please provide the consultant name and hospital details for the second hospital

GP Name: _____
GP Address: _____
_____

Consultant: _____
Hospital: _____
_____

Consultant (2): _____
Hospital (2): _____
_____

Appendix 7: Components of a disease cluster evaluation