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Pigbel in the 21st century: still here, and still in need of an effective surveillance system

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SUMMARY

Pigbel remains a likely significant cause of morbidity and mortality in the highlands of Papua New Guinea (PNG), two decades after the administration of pigbel vaccination ceased. There is a need for an effective surveillance program for pigbel to better understand the disease burden and to target communities for preventive strategies. This paper reviews the epidemiology, pathogenesis, recent history and current data on the burden of pigbel in PNG. We propose a surveillance program based on clinical recognition of likely cases and laboratory confirmation using an ELISA assay for *Clostridium perfringens* type C beta-toxin. Research aimed at validating this approach in the clinical setting is outlined.

Introduction

Pigbel is an intestinal infection caused by the beta-toxin of *Clostridium perfringens* type C, an anaerobic Gram-positive bacillus that proliferates in poorly cooked meat and occasionally other foods. It results in mucosal ischaemic ulceration of the bowel (1-3). Pigbel is not a new disease; under different names, it reached epidemic proportions in Germany and other European countries during and after World War 2, called *Darmbrand*, enteritis necroticans, enteritis gravitus or bacillus enterotoxicus (3). There have been sporadic reports of enteritis necroticans in other populations since World War 2, including in diabetic patients (4,5) and refugees (6,7), but pigbel is now rare outside Papua New Guinea (PNG).

Pigbel was an important cause of illness and death in children in PNG during the 1960s and 1970s. From 1961, when pigbel was first reported in PNG, until the early 1980s, pigbel was the second most common cause of death in children over one year of age in several hospitals in the PNG highlands (8,9). Following the introduction of a highly effective toxoid vaccine by Wellcome in 1979, a marked and apparently persistent decrease in cases was seen (10). In the 1960s, it had been thought that pigbel would disappear, as it had done in Europe, when living conditions improved. Production of the vaccine ceased in 1992. While it was widely believed that pigbel was no longer endemic, a study conducted in 2001 showed that pigbel caused between 9% and 16% of cases of acute abdominal pain in children presenting to health centres in the highlands and that there was substantial geographical clustering of cases on the Western Highlands-Enga provincial border (2).

In the 1990s, the Commonwealth Serum Laboratories (CSL, Melbourne, Australia) formulated for human use a new toxoid vaccine against pigbel. By October 1998 there were 300,000 doses produced, an estimated one-year supply (11). The vaccine remained

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in cold storage in Australia for several years, but at the time there was uncertainty about the true pigbel disease burden, where the vaccine would fit with other vaccination priorities in PNG and how and where it would be used. Because these issues were not resolved, the remaining stocks of the vaccine were discarded by CSL around 2002.

This paper provides a situation update for pigbel in 2013. We discuss the clinical features and disease causation, recent reports of pigbel from highlands provinces, the existing data and gaps, the need for a surveillance system and the possibility of a practical laboratory test for pigbel.

Pigbel disease causation and clinical features

Pigbel is characterized by acute abdominal pain (especially in the upper abdomen and made worse with eating), vomiting of blood or coffee grounds, bloody diarrhoea, abdominal distension and, in very severe cases, shock and collapse. After ingestion of *C. perfringens* type C, usually in poorly cooked meat, the clostridia proliferate in the gastrointestinal tract and release beta-toxin. The pancreatic enzymes trypsin and chymotrypsin can inactivate the toxin. If the toxin is not inactivated, it may cause segmental haemorrhagic, inflammatory or ischaemic necrosis of the jejunal and ileal mucosa. This is associated with toxaemia and is often fatal if untreated. The disease depends on exposure to the organism (a greater risk where there is a close association between people and pigs, and a poor level of hygiene) and consumption of a high-protein meal (frequently, but not always, pig). Predisposing factors include protein malnutrition (resulting in decreased pancreatic enzyme production), a staple diet of sweet potato (which contains pancreatic enzyme inhibitors) (8) and the presence of *Ascaris* roundworms in the intestine (which secrete anti-protease enzymes that protect them from being digested) (3). Early research on pigbel in PNG identified the following epidemiological factors (12):

- Gathering of large numbers of people, eating unhygienically slaughtered and improperly cooked meat
- Storing of half-cooked meat for days
- Consumption of large amounts of food of animal origin by a population living a nearly exclusively vegetarian diet at other times
- Left-over meat, kept for days and eaten by hungry children.

Data on current status

The current true incidence of pigbel is uncertain. National health information system data are unreliable and of uncertain accuracy. In the last decade, pigbel was more often reported from health centres and smaller hospitals than major provincial hospitals. In 2010-2012, only 3 cases of pigbel were reported from provincial hospitals participating in the Paediatric Hospital Reporting System. However, many cases have been reported from Nazarene Hospital at Kudjip in Jiwaka Province (Figure 1) and Kundiawa General Hospital, Simbu Province and there have been anecdotal or unconfirmed reports of pigbel outbreaks from other areas.

Pigbel shares many of the characteristics of other diseases under international surveillance, including poliomyelitis and measles: the acute flaccid paralysis (AFP) and acute fever and rash (AFR) surveillance programs, respectively. These common characteristics include their relatively low incidence, sporadic outbreaks, and the lack of specificity of clinical signs. Firstly, measles, polio and pigbel are much less common than, for example, pneumonia, malaria or diarrhoea. Secondly, most signs and symptoms are non-specific. To draw a parallel, most cases of AFP are Guillain-Barré syndrome, and many cases of AFR are not measles but other viral exanthems. Similarly, many of the cases of acute abdomen that could be pigbel are other diseases – typhoid, dysentery, worm infection, intussusception, urinary tract infection, appendicitis. These can be mistaken for pigbel by inexperienced health workers, and therefore a clinical diagnosis alone may over-report cases (2).

However, there are differences between pigbel and measles and polio in surveillance terms. Firstly, measles and polio are of international interest, so there is global support and political pressure for an effective surveillance program. Pigbel, on the other hand, has little or no international significance or recognition. Secondly, there is a confirmatory laboratory test for measles

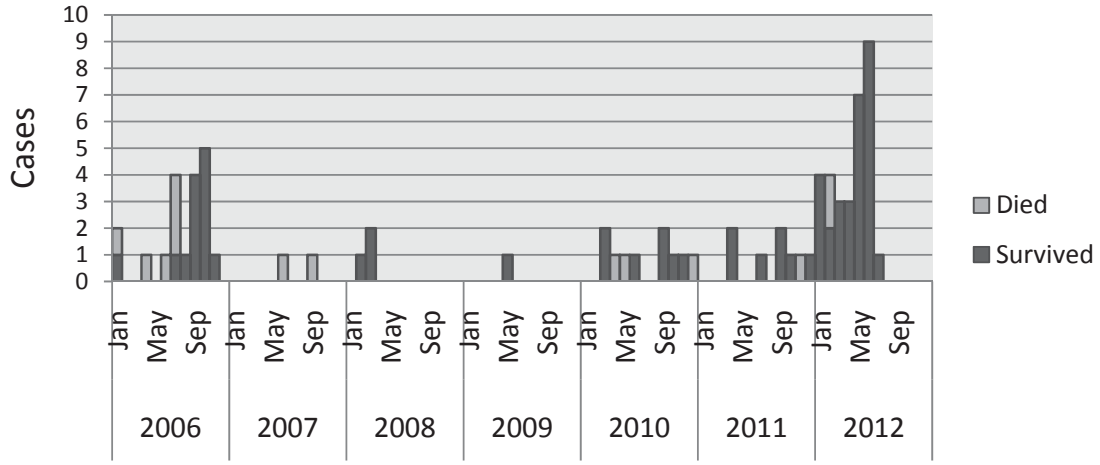

Figure 1. Cases of pigbel reported at Nazarene Hospital in Kudjip, Jiwaka Province, 2006-2012. All cases based on clinical diagnosis as recorded by the attending physician.

and polio, which transforms the non-specific clinical syndromic diagnosis into a specific microbiological or serological diagnosis. Until now there has been no such laboratory test for pigbel. Bacterial culture of *C. perfringens* type C – even where it is possible – is not a specific test, as asymptomatic children may have *C. perfringens* in stool; a study in Bangladesh showed *C. perfringens* type C in the stool of patients with watery or bloody diarrhoea, but no other signs of enteritis necroticans (13). It is not the bacterium per se that causes disease, but the beta-toxin.

A surveillance program and a new test

We propose that there should be a surveillance program for pigbel, similar conceptually to that for AFP and AFR. This would involve, firstly, identification of cases based on standardized clinical features and, secondly, a confirmatory laboratory test where this is available.

There is at least one ELISA assay for *Clostridium perfringens* type C beta-toxin (Bio-X Diagnostics, Rochefort, Belgium), which has been used in veterinary practice to diagnose haemorrhagic enteritis in sheep and goats (14,15). There are also anti-beta-toxin antibodies available for research use (eg, Abcam, Cambridge, USA) which could be further developed into clinical diagnostic tools. A test validated for diagnostic use in humans could provide confirmatory evidence of pigbel and enable more accurate surveillance and disease burden estimates. There is an urgent need to develop such a human diagnostic test or to evaluate an existing veterinary diagnostic test in a clinical research setting.

We are currently evaluating a surveillance system for pigbel that is based on a standardized clinical case definition (Table 1) and the Bio-X ELISA assay for beta-toxin. This study is taking place in the Nazarene and Kundiawa General Hospitals. This study will pilot this surveillance approach and determine the value of an assay for beta-toxin in the context of pigbel in PNG.

In the proposed surveillance program patients would be eligible for inclusion if they have had abdominal pain of less than 2 weeks' duration. Patients with diarrhoea and/or vomiting without abdominal pain would not be included. The case definition would be used to distinguish cases of acute abdominal pain very likely to be due to pigbel from cases very likely to be accounted for by other diagnoses (such as those listed in Table 1). The surveillance data form would also capture information about patient history, clinical course, medical and surgical management and laboratory results.

Children who may have pigbel on clinical grounds would have intestinal fluid (gastric fluid or stool) sampled and tested with the ELISA assay for *C. perfringens* beta-toxin. It is likely that, in pigbel, with the severe gastric paresis and often coffee-ground vomiting of stomach and small intestinal contents, the beta-toxin would be found in fluid aspirated by nasogastric tube. It may also be possible to find beta-toxin in the stool of patients with

TABLE 1

DIAGNOSTIC CRITERIA FOR SUSPECTED AND CONFIRMED PIGBEL

Clinical case definition for *suspected* pigbel:

Acute abdominal pain of less than 2 weeks' duration *plus* **three or more** of the following features:

- Meat meal eaten in the last 7 days
- *Severe* abdominal pain
- Pain most severe in the **upper abdomen**
- Pain worse with feeding
- Vomiting blood or foul material
- Upper abdominal distension or X-ray findings of multiple air-fluid levels
- Bloody diarrhoea
- Blood leukocytosis WCC >15,000/µl
- Toxic shock

Always consider **other possible diagnoses** in children or adults with acute abdominal pain: gastroenteritis, typhoid, dysentery, intussusception, appendicitis, urinary tract infection.

Final diagnosis is *confirmed* pigbel if:

- clinical case definition is positive, or
- a positive ELISA test for beta-toxin on gastric fluid or stool, or diagnostic intestinal lesions seen at surgery +/- histopathology

WCC = white cell count

pigbel; however, some of the toxin may be destroyed by trypsin and other proteolytic enzymes before being passed in diarrhoeal stool, so the yield from stool is uncertain and has not been tested in studies in animals with enteritis necroticans (14). Any patients undergoing surgery for suspected pigbel would also have a direct intestinal fluid sample taken.

Opportunities for prevention

With a better understanding of pigbel disease patterns through the use of a focused surveillance program, outbreaks could be confirmed and mapped, and effective prevention strategies could be put in place for the groups at highest risk. These strategies would also include community awareness and education about food preparation, the dangers of pigbel, the clinical symptoms of pigbel and when to seek care. Without an effective surveillance system, efforts to control pigbel will continue to be impaired by lack of accurate data, uncertainty about where best to put preventive efforts and what resources to use, lack of political will, and health worker ignorance about this disease and its treatment.

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