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Clinical and laboratory evidence of Haff disease – case series from an outbreak in Salvador, Brazil, December 2016 to April 2017

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We describe a series of 15 Haff disease cases from an outbreak in Salvador, Brazil, starting early December 2016. Eleven cases were grouped in four family clusters of two to four individuals, four were isolated cases. All but one patient consumed cooked fish; 11 within 24h before symptoms onset. Cases consumed 'Olho de Boi' (*Seriola* spp.) and 'Badejo' *(Mycteroperca* spp.). A total of 67 cases were detected, the last case was reported on 5 April 2017.

We describe a case series of Haff disease causing an outbreak in the city of Salvador, Brazil. The first case was reported on 1 December 2016 and here we present the clinical and epidemiological data of the first 15 cases of the 67 total cases detected as at 5 April 2017. On 14 December, after the identification of the first six cases, the local public health authorities began an active search for new cases in the health units and hospitals in Salvador and also searched medical records to retrospectively identify cases compatible with Haff disease back to July 2016. Structured interviews were conducted with every affected patient since the beginning of the outbreak.

Case definition

We defined cases as patients presenting with (i) sudden onset of muscle pain in more than two body regions e.g. superior limbs, inferior limbs, neck/trapezium region, back region, thorax and abdominal region, not related to intense physical activity; (ii) elevated levels of creatinine phosphokinase (CPK) (more than fivefold above the upper limit of the normal reference value of 170 U/L (i.e. 850 U/L) within 24 hours of presentation; and (iii) patients who recalled an ingestion of fish or fish products within 72 hours before the onset of symptoms.

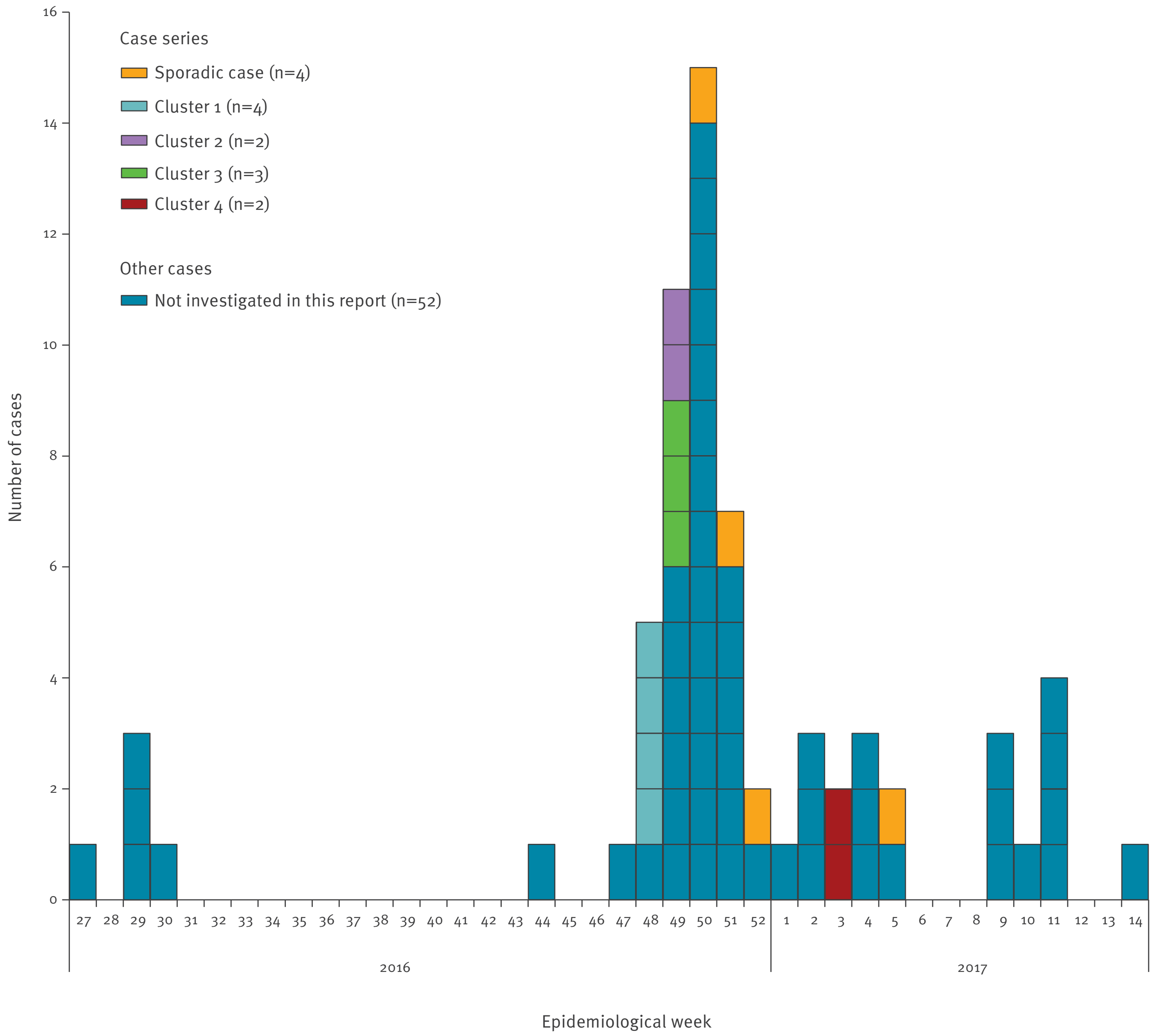
Laboratory investigations

Serial measurements of muscle enzymes, such as creatine phosphokinase (CPK), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) were performed in all patients. In addition, troponin I levels and creatine kinase-MB (CK-MB) fractions were measured in three and two cases, respectively.

We screened 10 patients for chikungunya and Zika virus RNA (serum n=4, urine n= 3, saliva n=3) given the significant circulation of both viruses in Salvador since 2015 [1,2]. RNA was extracted using QIAmp Viral RNA mini kit, according to manufacturer's instructions. Reverse transcription (RT)-PCRs were performed using standard protocols [3,4]. RT-PCR analyses were also performed for enteroviruses and Parechoviruses using reagents from AccessQuick (Promega), according to standard protocols [5-8]. Thirteen samples (serum and faeces) from eight patients were tested. Sequencing was performed by a sequencing facility using the ABI-Prism 3500 Genetic Analyzer (Applied Biosystems) on 40 ng of products and 2 pmol of each primer. The results were analysed with the help of the Basic Local Alignment Search Tool (BLAST).

Figure

Case series of reported cases of Haff disease according to the epidemiological week of symptoms onset, Salvador, Brazil, 1 December 2016–31 January 2017 (n=15)



The figure shows Haff disease cases identified retrospectively and prospectively after recognition of the outbreak.

Pieces of uncooked fish ('Olho-de-Boi') from one patient were sent for toxin analysis at the Food and Drug Administration (FDA), in the United States (US), through the Brazilian Ministry of Health.

Outbreak description

The outbreak started on 1 December 2016 with a family cluster of four patients who presented to the emergency department (ED) within less than 24 hours with sudden onset of muscle pain in different body parts, initiated at the trapezium area, and followed by dark urine in two. They all had consumed the same fish products 12 to 72 hours before symptoms onset and all had highly elevated muscle enzymes, compatible with rhabdomyolysis. Eight days later, two other non-linked family clusters of three and two individuals, respectively, came within hours to the ED with a similar history of ingestion of fish and symptoms of rhabdomyolysis. Within each cluster, all patients had consumed the same fish. During the following three weeks, three more cases (comprising another family cluster of 2 cases) presented the same symptoms, had the same history of fish ingestion, summing up to 12 cases by 28 December 2016. In January 2017, three further cases were diagnosed, adding up to the 15 cases studied in detail and presented here.

Table 1

Demographic and clinical characteristics of cases in outbreak of Haff disease, Salvador, Brazil, 1 December 2016–31 January 2017 (n=15)

Characteristics	Number or median (range)
Male	9
Age, years	43 (14–75)
Symptoms/signs at first medical care[a]	
Neck/Trapezium pain	14
Arms pain	14
Thighs or legs pain	13
Back pain	10
Thoracic pain	2
Abdominal pain	2
Throat pain	1
Muscle weakness	6
Fever	0
Rash	4
Dark urine	8
Vital signs	
SBP, mmHg[b]	146 (110–168)
DBP, mmHg[b]	79 (60–89)
Heart rate, bpm[b]	74 (60–97)
Comorbidities[a]	
Arterial Hypertension	1
Hyperlipidaemia	2
Type II diabetes mellitus	1
Chronic atrial fibrillation	1
Depression	2
Hypothyroidism	1
Patients on statin therapy	2
Outcome	
Hospitalisation	13
Acute kidney injury	2
Death	0

Bpm: beats per minute; DBP: diastolic blood pressure; SBP: systolic blood pressure.

[a] Patients may present with more than one comorbidity or symptom/signs.

[b] Data available for 11 patients.

The majority of the 15 cases of Haff disease reported here clustered between the epidemiological week 48 and 51 of 2016, however, new cases continued to be reported up to epidemiological week 14 of 2017 (Figure). After the recognition of the outbreak in December 2016, local health authorities started an active search for cases and they identified similar cases admitted to local hospitals in Salvador back in July 2016.

The median age of the first 15 cases was 43 years (range: 14-75), there were slightly more men (n=9) than women (n=6), and all cases reported sudden onset of muscle pain, particularly, pain in the neck or trapezium regions was reported by 14 patients. Eight patients reported dark urine compatible with myoglobinuria and a mild rash was seen in four. At initial medical care or during hospitalisation, none of the cases presented with fever, arthralgia, respiratory, or gastrointestinal symptoms, except for two patients who reported transient loose stools. Six patients had comorbidities. Thirteen patients were hospitalised with a median hospital stay of 3 days. Clinical and demographic variables are shown in Table 1.

CPK levels at presentation ranged from 743 to 105,755 U/L and decreased rapidly on subsequent days in parallel with the improvement of symptoms. Troponin I levels were less than 0.034 ng/mL in all patients with measurements. CK-MB fraction ranged from 1.9% to 6.3%.

RT-PCR for chikungunya and Zika viruses, as well as nested RT-PCR for Parechovirus, yielded negative results for all patients in all types of samples. The RT-PCR for enterovirus generated non-specific products in four samples. However, upon analysis of the sequenced fragments no virus could be identified.

Epidemiological links, food consumption history and symptom onset

In the interviews, patients were asked about possible links to other cases, fish consumption and the timely relation to symptom onset. Eleven cases were grouped in four family clusters of two to four individuals and four were isolated cases. One limitation of the present study is that we did not investigate all family members to determine the attack rates within clusters. Table 2 shows the clustering pattern for the cases, as well as the species of fish consumed by each of them, and the time elapsed between fish ingestion and symptom onset. All but one case had consumed cooked fish. Time between consumption and onset of symptoms ranged between 2 to 5 and 72 hours. Of the 14 cases who reported fish consumption, 11 had ingested fish within 24h before symptoms onset.

The species of seawater fish consumed were 'Olho de Boi' (*Seriola* spp) and 'Badejo' (*Mycteroperca* spp). One case had reportedly not eaten fish, but eaten a local Afro-Brazilian dish with possible fish by-products used in its preparation within 24 hours of symptoms onset.

Analysis of the fish sample by the FDA revealed no toxins or heavy metal contamination.

Background

Cases of Haff disease were first described in 1924, in the Baltic region of Prussia and Sweden and involved the consumption of different cooked freshwater fish, such as burbot (*Lota lota*), pike (*Esox* sp.) and freshwater eel (*Anguilla anguilla*) [9]. In the US, the first cases of Haff disease were reported in Texas in 1984, and hereafter the Centers for Disease Control and Prevention (CDC) reported six additional cases of Haff disease in patients from California and Missouri, who had eaten buffalo fish [10]. In 2001, two cases were

Table 2

Case clustering, species of fish consumed, and time elapsed between fish ingestion and initial symptoms onset for case series of Haff disease patients, Salvador, Brazil, 1 December 2016–31 January 2017 (n=15)

Case number	Cluster number	Type of fish consumed	Time elapsed between fish ingestion and symptoms onset
Case 1	Cluster 1	A+B	48 – 72 hours
Case 2	Cluster 1	A+B	48 – 72 hours
Case 3	Cluster 1	A+B	12 – 24 hours
Case 4	Cluster 1	A+B	48 – 72 hours
Case 5	Cluster 2	B	21 hours
Case 6	Cluster 2	B	11 hours
Case 7	Cluster 2	B	7 hours
Case 8	Cluster 3	A	12 hours
Case 9	Cluster 3	A	13 hours
Case 10	No cluster	B	10 hours
Case 11	Cluster 4	Unknown[a]	7 hours
Case 12	Cluster 4	Unknown[a]	6 hours
Case 13	No cluster	A	10 hours
Case 14	No cluster	None[b]	NA
Case 15	No cluster	A	2 – 5 hours

A: 'Olho de Boi' (*Seriola* spp.); B: 'Badejo' (*Mycteroperca* spp); NA: not available.

[a] Unknown type of fish consumed.

[b] Case 14 reportedly did not consume fish, but ate local Afro-Brazilian food, which might have fish by-products used in its preparation.

identified in North Carolina who had eaten baked Atlantic salmon [11] and in 2014, further individual case reports were published, both cases developed symptoms after the ingestion of buffalo fish [12,13]. In 2010, China reported cases associated with the ingestion of crayfish [14].

In Brazil, an outbreak of 27 cases of Haff disease occurred during 4 months in the northern state of Amazonas in 2008 [15] and an additional case from the Amazon region was reported in 2013 [16].

It is considered that the condition is due to an unknown toxin in the aquatic food chain.

Discussion

We describe a cases series in an outbreak of Haff disease in Salvador that involved 15 patients as at 31 January 2017 with the majority of them clustered in families. An earlier outbreak of Haff disease in our country was reported in the Amazon region in 2009. It was related to ingestion of three different species of freshwater fish present in the Amazonian rivers [15] and authors identified the same pattern of family clusters as observed by us [15].

An important limitation of case series is the methodological limitation concerning risk factor analysis and the control of possible confounders. However, the sudden onset of similar symptoms in family clusters, a few hours after consumption of the same food, point to a common exposure. The absence of fever and gastrointestinal symptoms and laboratory signs of infection (data not shown) led us to hypothesise an ingested toxin as the cause. Given the universal ingestion of fish or its by-products by all cases and the compatibility with the described Haff syndrome, we considered a fish toxin as the most probable cause of illness in our case series.

After its recognition, seven cases of Haff disease were retrospectively identified back to July 2016, and 60 cases have been reported since 1 December 2016, totalling 67 cases reported in this outbreak until now. The last case was reported on 5 April 2017 [17].

'Olho de Boi' (*Seriola* spp.) and 'Badejo' (*Mycteroperca* spp.) are seawater fish. Palytoxin is a toxic substance present in some soft corals (*Palythoa* sp.) and analogues were also isolated from dinoflagellates of the genus *Ostreopsis* that are vastly distributed in tropical water throughout the world, including the coast of Brazil [18]. Our patients did not present with typical manifestations of palytoxin intoxication i.e. chest pain, shortness of breath, wheezing, tachycardia, although two patients reported episodes of loose stools (diarrhoea may occur in palytoxin intoxication) and all had myalgia and rhabdomyolysis, a common feature of palytoxin intoxication related to the Na+-K+-ATPase binding effect. Samples of fish consumed by one of our patients were analysed for ciguatoxin by the FDA with negative results. This is not surprising in the face of the difficulty in isolating the aetiological toxin involved. In 21 similar cases in the US, where samples of suspected fish or seafood were tested by the CDC or the FDA, all were negative for different aquatic toxins, including ciguatoxin, saxitoxin, brevetoxin, tetrodotoxin, palytoxin, and cyanobacterial toxins [19].

It is important for travel medicine physicians to be alert in case of patients returning from Salvador, Brazil, with myalgia and symptoms of rhabdomyolysis to consider Haff disease as a possible differential diagnosis. Care should also be taken when treating these patients so as to avoid non-steroidal anti-inflammatory agents because of possible concurrent renal toxicity [20].

Conflict of interest

None declared.

Authors' contributions

Antonio C Bandeira - literature search, data collection, tables, figures, data analysis, data interpretation, writing.

Gubio S Campos - literature search, molecular methods, data analysis, data interpretation.

Guilherme S Ribeiro - literature search, data analysis, tables, data interpretation, writing.

Cristiane W Cardoso - literature search, data collection, data analysis, data interpretation, writing.

Claudilson J Bastos - data collection, data interpretation.

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Rejane H Carvalho - literature search, molecular methods, data analysis.

Ana Paula P Prates - data collection, writing.

Luana L Gois – literature search.

Veronica FD Rocha - literature search.

Silvia I Sardi - literature search, molecular methods, data analysis.

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Surveillance and outbreak report

Botulism in Italy, 1986 to 2015

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Botulism is a rare but severe neuroparalytic disease caused by botulinum toxins. Because of its high potential impact on public health, botulism is a closely monitored communicable disease in Europe. In Italy, which has one of the highest incidence rates in Europe (0.03 cases per 100,000 population), botulism is monitored through a case-based passive surveillance system: the front-line physician who diagnoses a suspected case must notify the Local Health Units immediately, and the Ministry of Health's office within 12 hours. From 1986 to 2015, 466 confirmed cases of botulism were recorded in Italy (of 1,257 suspected cases). Of these, 421 were food-borne (the most frequently seen form of botulism due to the consumption of improperly home-canned foods), 36 were infant botulism, which accounts for ca 50% of all these types of cases registered in Europe, six were wound-related and three were due to adult intestinal colonisation. This scenario suggests that stronger efforts should be made towards raising public awareness of the risk of food-borne botulism, especially with respect to home-preserved foods, as well as improving the training of front-line medical personnel, to ensure that a quick and accurate diagnosis of botulism can be made.

Introduction

Botulinum neurotoxins (BoNTs) are the most potent poisons known [1,2]. Due to their formidable potency BoNTs can be used as biological weapons. Because of the potentially high public health impact, the occurrence of botulism cases and outbreaks is closely monitored. All seven antigenic variants of BoNTs identified to date (A to G) act on presynaptic neurons, blocking the release of the neurotransmitter acetylcholine in the neuromuscular junctions. Botulism onset may include a prodromal phase, characterised by gastrointestinal discomfort and anticholinergic symptoms such as xerostomia (dry mouth), while the typical final syndrome consists of a symmetrical cranial nerve palsy, followed by symmetrical descending flaccid paralysis of both voluntary and autonomic muscles [1-4]. The diagnosis of botulism is based on clinical examination and confirmed by laboratory testing [1,2]. The treatment of the disease includes administration of botulinum antitoxin serum and, when required, support of respiratory function [1,2]. Different formulations containing varying quantities and combinations of specific types of antitoxins are used worldwide. Serum available in Italy is distributed by the Ministry of Health (MoH) and consists of 250 ml of trivalent equine antitoxin, protecting against BoNTs of type A, B, and E. The recommended dose is two vials; each vial contains 187,500 IU against-BoNT/A, 125,000 IU against-BoNT/B and 12,500 IU against-BoNT/E [2].

BoNTs are produced *Clostridium botulinum* and also by rare strains of *Clostridium baratii* and *Clostridium butyricum* [2-4].

To date, six forms of botulism are recognised and classified according to the modality of exposure to the toxin [2,5]: (i) Food-borne botulism occurs after the ingestion of preformed BoNT in food [6]; both (ii) infant botulism and (iii) adult intestinal colonisation (also collectively referred to as intestinal toxaemia botulism) are caused by the ability of spores to germinate in the colon, producing BoNTs in situ; (iv) wound botulism is the consequence of in vivo toxinogenesis of *C. botulinum* spores contaminating an injury [1]; (v) iatrogenic botulism is a complication of the treatment with BoNTs for therapeutic or cosmetic use [1] and (vi) inhalation botulism, results from accidental or deliberate release of aerosolised toxins [1,5]. Iatrogenic and inhalation botulism are the two non-naturally occurring forms [5].

Although botulism is a rare disease worldwide, the Italian incidence rate is one of the highest in Europe, ranging between 0.02 and 0.04 cases per 100,000

Figure 1

Suspected (n=1,254) and laboratory-confirmed cases (n=466) of botulism, Italy, 1986–2015

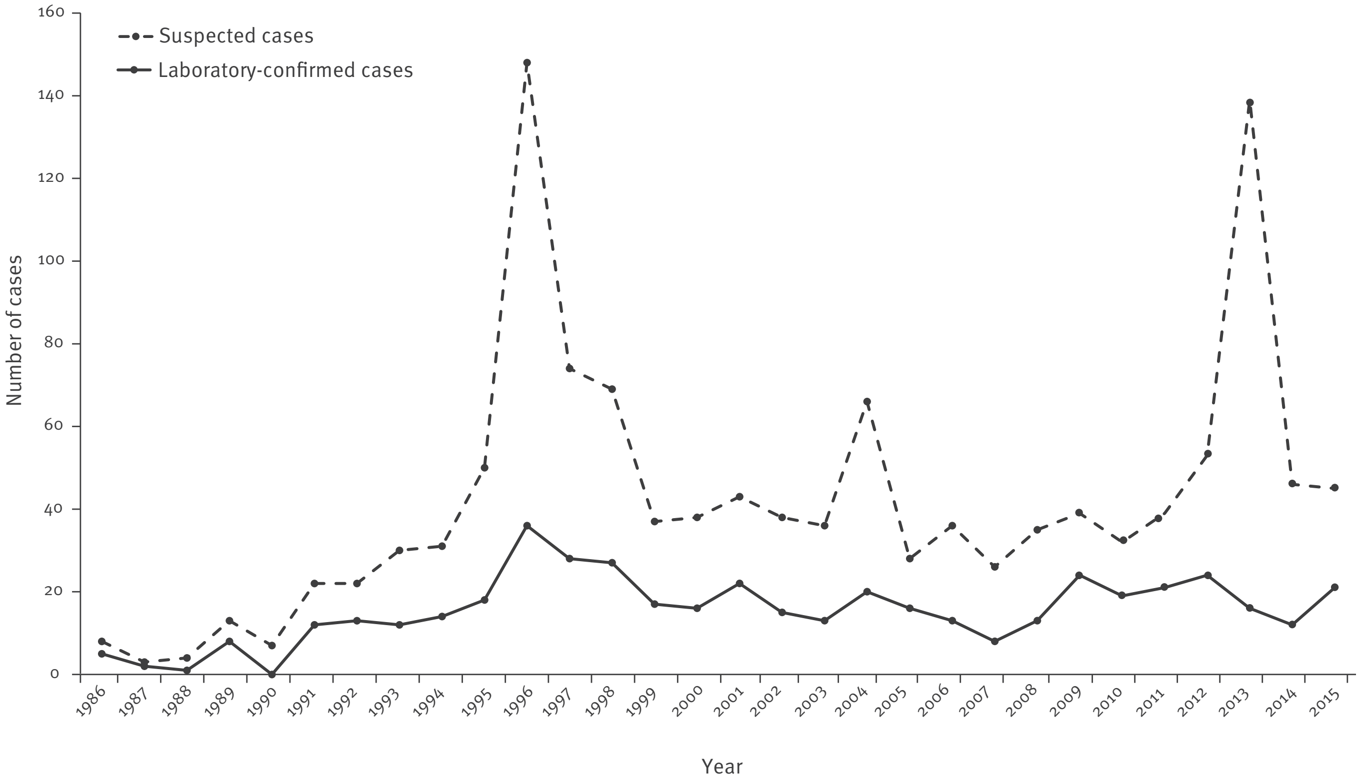

Figure 2

Annual incidence of botulism per 100,000 population, Italy, 1986–2015 (n=1,254)

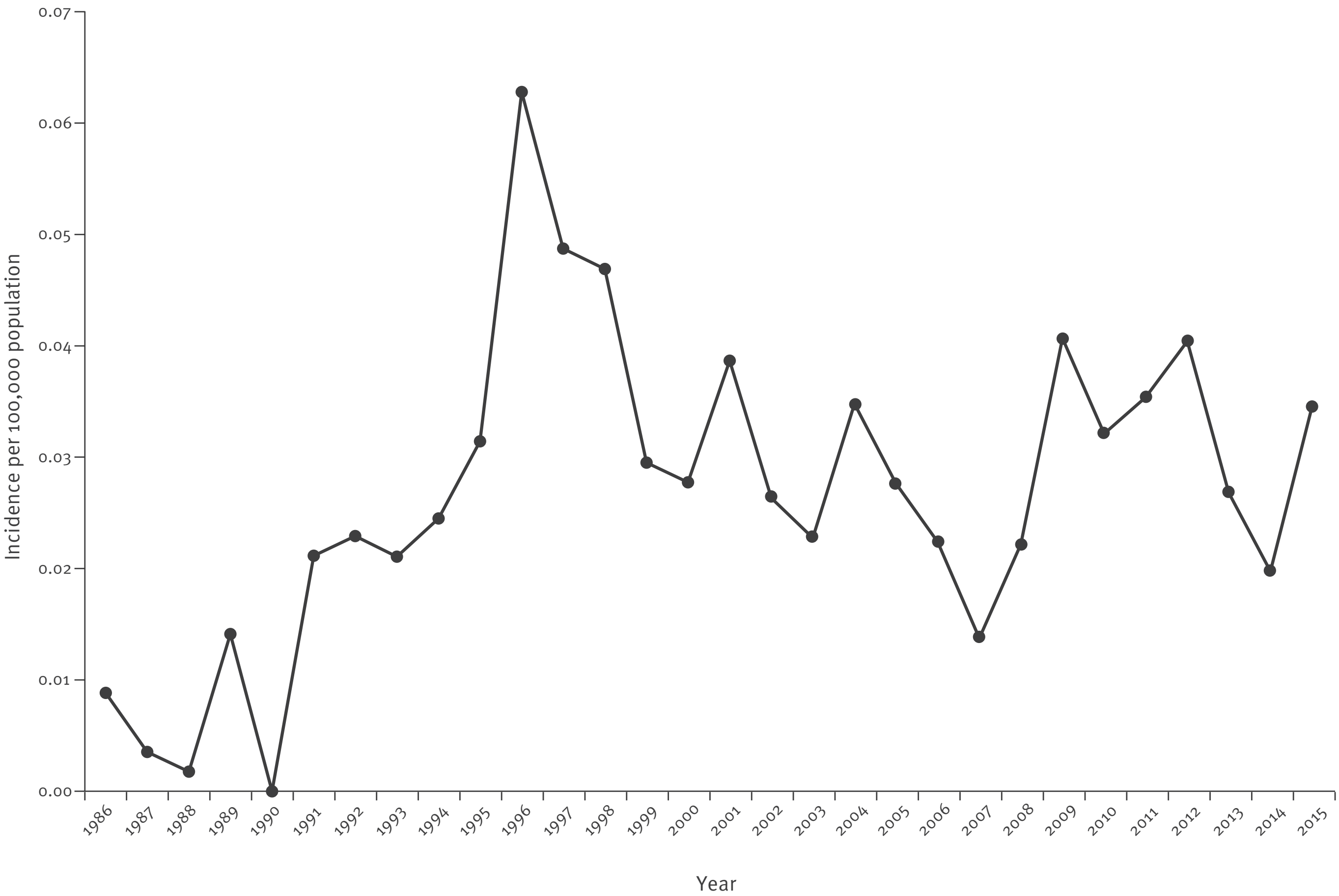

Table 1

Number and percentage of suspected and laboratory-confirmed cases by type of botulism, Italy, 1986–2015

Type of botulism	Suspected cases			Laboratory-confirmed cases		
	Number	%	95% CI	Number	%	95% CI
Food-borne	1,173	93.3	91.9 to 94.7	421	90.4	87.7 to 93.0
Infant	70	5.6	4.3 to 6.8	36	7.7	5.3 to 10.1
Wound	9	0.7	0.2 to 1.2	6	1.3	0.3 to 2.3
Adult intestinal colonisation	5	0.4	0.0 to 0.7	3	0.6	−0.1 to 1.4
Total	**1,257**	**100**	**NA**	**466**	**100**	**NA**

CI: confidence interval; NA: not applicable.

population from 2006 to 2010 [7,8]. All of the naturally occurring forms of botulism are represented, and although food-borne botulism is the prevalent form, the number of infant botulism cases reported in Italy represents ca 50% of all European cases [8,9].

Here we provide detailed information on epidemiological features of clinical cases and outbreaks of botulism in Italy from 1986 to 2015.

Material and methods

Surveillance system

In Italy, the MoH included botulism as a notifiable disease in 1975, and it became a Class I disease, i.e. one requiring immediate reporting, in 1990 [10]. The current reporting system requires the front-line physician to notify Local Health Units immediately of all suspected cases, and then proceed with notifying the Regions, the MoH and the Istituto Superiore di Sanità (ISS), National Reference Centre for Botulism (NRCB) and National Centre for Epidemiology, Surveillance and Health Promotion within 12 hours of their initial formulation of clinical suspicion [11]. The NRCB and other accredited local laboratories receive clinical samples for laboratory testing the results of which are sent to the physician in charge of the case and the MoH. The MoH, in collaboration with the NRCB, collects all data and transmits them to the European Centre for Disease Prevention and Control (ECDC). Pavia Poison Control Centre (PPCC) provides expert clinical advice for acute clinical management, including indications for antitoxin administration, and performs a targeted clinical follow-up for possible late complications or adverse effects (e.g. serum sickness).

Case definitions

From 1975 to 1991, no standard case definition of botulism was used in Italy, while from 1991 to 1996 the MoH adopted the case definitions published by the United States Centers for Disease Control and Prevention (CDC) [12]. According to these, only laboratory-confirmed cases were classified and reported. On 1 July 1996, the MoH amended the definition publishing the Circular Number 9 laying down the 'Misure di prevenzione e controllo delle intossicazioni da botulino' (measures for prevention and control of botulism) [13]. In 2002, the European Commission adopted Decision 2002/253/EC aimed at standardising case definitions of communicable diseases among Member States [14]. Unlike the previous definitions used in Italy, the first European case definitions made no distinction among the different forms of botulism, although confirmed cases (defined as clinically compatible cases confirmed in the laboratory) were marked as different from probable cases (defined as clinically compatible cases with an epidemiological link) [14]. This latter decision was amended in 2003, 2008 and 2009. The current definitions categorise botulism into two clinical forms: (i) food-borne and wound botulism and (ii) infant botulism; cases are classified as probable or confirmed [15].

For the purposes of this work, the occurrence of a sporadic case or an outbreak of food-borne botulism is defined as an incident.

Data collection and analysis

Demographic, clinical and epidemiological data were obtained from the patient by the attending physician using a specific notification form, which is sent to both the NRCB and the MoH. Additional epidemiological investigations may be performed by the Department of Hygiene and Public Health and Local Health Units and additional information collected by the NRCB during phone interviews with patients and relatives and/or by the PPCC during patient clinical follow up. All these data, together with the microbiological and laboratory analyses results, are collected and stored in a specific database by the NRCB, which transmits all data to the MoH annually.

Statistical analysis was performed using Microsoft Excel 2010 (Microsoft Corp., US) and Prism version 6.03 (GraphPad Software, Inc., La Jolla, CA, US) by univariate analysis with chi-squared and t tests, as appropriate. A result of $p < 0.5$ was considered to indicate statistical significance.

Table 2
Number of laboratory confirmed cases by regions and type of botulism, Italy, 1986–2015 (n=466)

Region	Food-borne botulism	Infant botulism	Wound botulism	Adult intestinal colonisation botulism
Piemonte	20	0	1	1
Valle d'Aosta	0	0	0	0
Lombardia	21	5	0	0
Trentino Alto Adige	4	0	0	0
Veneto	19	4	0	1
Friuli Venezia Giulia	15	2	0	0
Liguria	14	0	0	0
Emilia Romagna	28	2	0	1
Toscana	4	0	0	0
Marche	6	0	0	0
Umbria	9	1	0	0
Lazio	43	11	1	0
Sardegna	10	0	0	0
Abruzzo	11	0	1	0
Molise	4	0	0	0
Campania	71	6	0	0
Basilicata	15	0	0	0
Puglia	58	4	1	0
Calabria	39	1	0	0
Sicilia	30	0	2	0
Total	**421**	**36**	**6**	3

Laboratory investigations

Clinical specimens for laboratory confirmation are taken by the attending clinician as soon as a diagnosis of botulism is suspected, and are sent for testing as soon as possible. Arrangements for testing leftover food are also made as a matter of urgency. If necessary, other foods are collected and sent for testing during any further epidemiological investigations by Local Health Units (Departments of Hygiene and Public Health). The NRCB carries out at least 90% of laboratory diagnosis performed in Italy, using analytical methods accredited according to ISO 17025 [16]. Detection of BoNTs was carried out by mouse bioassay, while detection of BoNT-producing *Clostridium* was carried out through multiplex real-time PCR developed and validated by the NRCB [17,18].

Results

From 1986 to 2015 a total of 1,257 suspected cases of botulism were notified to the NRCB. Of these, 466 cases were laboratory-confirmed (Table 1).

Male patients represented 51.7% of the confirmed cases (241/466) while females represented 45.7% (213/466) of cases. For the 12 remaining patients, sex was not reported.

Overall, the number of both notified and confirmed cases increased from 1986 to 1994, with an average of 40 notifications and 15 confirmations per year. The largest peak in notification of suspected cases was observed in 1996 as a consequence of four outbreaks due to commercial foods (mascarpone cheese and olives), and in 2013 as a consequence of a suspected outbreak due to commercial pesto sauce (Figure 1). The average annual incidence during the entire surveillance period was 0.03 per 100,000 population (range: 0.00–0.06), see Figure 2.

Ninety-six percent (316/330) of the laboratory-confirmed incidents were due to the neurotoxin produced by proteolytic strains of *C. botulinum*. Type B toxin was implicated in 79.1% (261/330) of all confirmed incidents, followed by type A (9.7%, 32/330), and type F, Ab and Bf toxins, accounted for 0.3% (1/330), 1.5% (5/330) and 0.6% (2/330) of the total incidents, respectively.

No clear seasonal pattern was observed for food-borne botulism, although during the holiday periods (Christmas, Easter and August holidays) the number of suspected cases usually increased. Conversely, a seasonal pattern was detected for infant botulism: 11 of 36 confirmed cases occurred in April, an observation which has yet to be explained.

Food-borne botulism

From 1986 to 2015, 285 laboratory-confirmed incidents involving a total of 421 persons were recorded.

Table 3

Clinical signs and symptoms reported by patients with food-borne botulism, Italy, 1986–2015 (n=421)

Clinical sign/symptom	Number of cases	% of cases
Headache	28	6.6
Double vision	298	70.6
Drooping upper eyelid	43	10.2
Dilation of the pupil	88	20.9
Difficulty in swallowing	304	72.0
Dry mouth	278	65.9
Facial palsy	28	6.6
Respiratory failure	75	17.8
Constipation	209	49.5
Nausea	145	34.4
Vomiting	157	37.2
Abdominal pain	6	1.4
Diarrhoea	40	9.5
Urinary retention	20	4.7
Coma	9	2.1
Death	17	4.0

The mean number of cases per incident was 1.5 (range: 1–16 cases per incident).

Most confirmed incidents, involving 241 persons in total, originated in rural areas of central and southern regions of Italy (Table 2), and in particular in Campania (50/285, 17.5%), Puglia (40/285, 14.0%), Lazio (31/285, 10.9%), Sicilia (22/285, 7.7%), and Calabria (21/285, 7.4%).

In these areas, many people still maintain the tradition of preparing home-canned foods, due to the low cost and wide availability of raw food materials. In the 10 years to 2015, an increasing number of cases were reported in Emilia Romagna, Lombardia and Piemonte (northern Italy). More than 90% of these cases involved university students (mostly male) of southern Italian origin, who had consumed homemade canned food prepared by their mothers.

The median age of cases was 43 years (range: 0–93 years) during the entire surveillance period: 49.2% of patients (207/421) were in the 25–65 years age group, 51.3% (216/421) were male.

Hospitalisation and clinical symptoms

Although all patients were admitted to hospital, length of hospitalisation was unknown because the reporting system did not record this information or the medical follow up. As reported in Table 3, dysphagia was the most common clinical symptom (304/421, 70.6% of cases).

Usually, patients presented mild symptomatology, with a clinical picture including diplopia (double vision), dysphagia (difficulty in swallowing), and dry mouth in ca 50% of the cases. Respiratory failure was reported in 17.8% (75/421) of patients. As for gastrointestinal symptoms, vomiting was reported by 37.3% (157/421), nausea by 34.4% (145/421), and diarrhoea by 9.5% (40/421) of the patients. A total of 16 deaths were recorded, giving a case-fatality rate of 3.8% (16/421), with four of the deaths occurring in elderly patients aged over 80 years who lived alone. The highest numbers of deaths were seen in 1996 and 2005, with three and four deaths respectively. Type B (11 cases), A (4 cases), and Ab (1 case) neurotoxins were detected in clinical specimens from the cases who died.

Botulinum antitoxin administration

Data on botulinum antitoxin administration were available from 1995 onwards, for 300 patients: Of these, 162 (54.0%) received the antitoxin. Although the manufacturer-recommended dose is two vials, 71/162 patients (43.8% of all those who received the antitoxin) were treated using different dosages. In particular, 46 patients received half the dosage recommended by the producer. No cases of adverse reactions to the antitoxins have been reported through the official botulism surveillance system; however, the Pavia Poison Control Centre reported that of 59 patients treated from 2007 to 2015, six showed adverse reactions.

Laboratory investigations

Serum was tested for 65.3% of patients (275/421) of confirmed food-borne cases and resulted positive only for 20.4% of them (56/275). The remaining cases were confirmed by direct detection of toxins in faecal samples (52 patients) or foods (159 patients). A further 154 food-borne cases presenting with the characteristic clinical picture of botulism were laboratory-confirmed, with BoNT-producing *Clostridium* isolated from faecal samples.

Food items involved

Food was identified as the transmission vehicle either by laboratory testing or following epidemiological investigations in 41.4% (118/285) and 30.7% of all confirmed incidents (86/285), respectively. A total of 80.5% (95/118 incidents, involving 143 persons) of food items linked to confirmed incidents consisted of homemade canned food, while the remaining 19.5% (23/118) was commercial food. Only one outbreak was connected to restaurant-canned green olives. Vegetables canned in oil and in brine/water were associated with 43.2% (51/118) and 28.8% (34/118), respectively, of laboratory-confirmed incidents. Other types of food related to laboratory-confirmed incidents were home-bottled tuna (9/118, 7.6%), ham (7/118, 5.9%), home-bottled meat (7/118, 5.9%), salami/sausages (5/118, 4.2%), cheese (3/118, 2.5%) and tofu and seitan (2/118, 1.7%). Among vegetables, the most frequent products involved in cases or outbreaks were mushrooms in oil (27 incidents involving 40 people), olives (eight incidents, 19 cases) and turnip tops (eight incidents, 17 cases). The most common food not analysed in the laboratory but connected to incidents via epidemiological investigations was vegetables in oil (51/86, 59.3%) and vegetables in water/brine (21/86, 24.4%). Of these, mushrooms were linked to 19 incidents (21 patients), leafy vegetables to eight incidents (eight patients) and peppers to six incidents (six patients). In Italy, meat products are rarely linked to botulism. Of 18 incidents connected to these products, 16 were due to consumption of home-prepared foods. From 1986 to 2000 these home-prepared products were most often improperly preserved ham and sausages, while from 2001 to 2015 to the most representative infection vehicle was home-bottled meat brought in to Italy by Eastern European workers. Interestingly, the latter exclusively involved males and often occurred after visits home to native countries for Christmas when it is common to return with traditional home-bottled foods. A combination of improper preparation and storage of jars were at the basis of these incidents. Regarding fish products, home-canned tuna was the most common food linked to confirmed incidents. Cheese or dairy products were seldom associated with confirmed incidents, even though the most well-known botulism incident ever to occur in Italy was related to mascarpone cheese [19].

Intestinal toxaemia botulism

From 1986 to 2015 only three cases of adult intestinal colonisation botulism were reported in Italy, in two males (a 9-year-old boy and a man in his mid-50s) and one female (19 years old). *Clostridium butyricum* capable of producing type E toxin was recovered in the faecal samples of the 9-year-old male and the 19-year-old female, while *C. botulinum* type A was recovered from the faecal samples of the other patient. The patients whose botulism was due to *C. butyricum* type E had serious gastrointestinal symptoms with acute pain, and both underwent surgery for suspected appendicitis. The neurological symptomatology was initially mild, but worsened rapidly after the surgery and both patients required mechanical ventilation. During surgery, both patients were found to have a Meckel's diverticulum. Following the surgery the male patient was treated with rifampicin while the female patient with ceftazimide. The third patient, a man in his mid-50s, was admitted to hospital with diplopia, dysphagia, nausea and vomiting with no fever. Thirty days before the hospitalisation he had undergone heart surgery and received postsurgical antibiotic therapy consisting of ceftriazone for 2 days. Approximately 1 month after heart surgery the neurological symptoms persisted and *C. botulinum* type A was recovered by stool cultures. As potential suspected food items could not be identified as being consumed by the patient and yet *C. botulinum* persisted in the intestinal tract for at least 6 weeks, adult intestinal colonisation botulism was diagnosed.

Infant botulism

From 1986 to 2015, a total of 36 cases of infant botulism (17 boys and 19 girls) were laboratory-confirmed. In all 36 cases, the patients were hospitalised: 20 infants received parenteral feeding and 13 required mechanical ventilation because respiratory failure had occurred. The length of the hospital stay was known only for 27 infants, reporting an average of 33.6 days (median = 28.0 days). One boy stayed in hospital for over 150 days. The average age at hospital admission was 16.2 weeks (range: 4–33 weeks). Before symptom onset, all infants had been in good health: 26 infants had been breast-fed, two had been formula-fed, and eight had been both breast- and formula-fed; 12 of them had started weaning. Honey consumption and herbal infusion was reported for 20 and nine infants, respectively. Nineteen patients received broad-spectrum antibiotics because severe infection was suspected before an infant botulism diagnosis was made. Nine infants were treated using equine botulinum antitoxin to avoid worsening of the symptoms. The first four patients received an amount of 40 ml/kg, 23 ml/kg, 16 ml/kg and 10 ml/kg per body weight of equine-derived antitoxins (see food-borne botulism section), respectively. The others received a dosage 10 ml/kg per body weight. No adverse effects to equine antitoxin were recorded for any patient.

All cases were laboratory confirmed and neurotoxigenic strains were isolated as *C. botulinum* type B in the faeces of 26 infants, *C. botulinum* type A in 5 and type E *C. butyricum* in three other cases. The remaining two cases were due to type Ab and Bf *C. botulinum*, respectively. Faecal specimens were tested for BoNT in only 23 cases (for the others, only rectal swabs were tested) and gave positive results in 17 infants (13 type B, 3 type A, and 1 type E). Due to the low amount of stool received for testing, a spore count was performed on only 12 samples, obtaining a range from 21 to 1,000,000 spores per gram. The testing for persistence of spores in the intestinal tract of patients was routinely performed by the NRCB, which collected samples every 2 days. In these 36 patients, spores persisted for an average of 18.5 days (range: 7–97 days). For 23 infants, food (honey and herbal infusion) and other environmental samples were collected from their homes and examined for BoNT-producing *Clostridium*. Five honey samples were positive but the strain isolated was of a different toxin type to that isolated from the infants.

Wound botulism

In Italy, the first case of wound botulism was diagnosed based on clinical observation in 1976. From 1986 to 2015, six cases were reported. Except for one case involving a drug user, all remaining cases were due to traumatic injuries (accidental falls or other accidents at work). All patients were adults (mean age 43.7 years old, range: 24–61 years), five were male and one was female. Neurological symptoms occurred a mean 10.3 days after the injury (range: 7–17 days), including ptosis (drooping of the upper eyelid), mydriasis (pupil dilation), diplopia and dysphagia in all seven patients, constipation and respiratory failure in three cases, and fever in two cases. Antibiotic therapy was administered to six patients: ampicillin combined with cephalosporin, netilmicin, amoxicillin and clavulanate, ciprofloxacin, metronidazole, ertapenem, and ceftriaxone were the drugs most frequently used (alone or in combination). Antitoxin therapy was administered to four patients, with adverse reactions noted in only one of them. Finally, hyperbaric oxygen treatment of the injury was used for one patient in 1991.

All cases were laboratory-confirmed by means of BoNTs detection in serum (5 patients) and through the isolation of BoNT-producing strains from wound exudate. Five of the six cases were due to type B botulism; in the remaining case, the type of toxin was not determined.

Discussion

Botulism remains a public health concern because of its severity and epidemic potential, as well as its possible use as a biological weapon. In Italy, food-borne botulism due to traditional home-canned food still represents a public health challenge mainly in the southern regions, where improper canning procedures are the primary reason for the occurrence of cases and outbreaks. On the contrary, cases due to refrigerated processed food with extended durability are concentrated in northern regions, where home-canning of foods is less common [10]. Since improper storage conditions seem to be the most frequent cause, permitting BoNT-producing *Clostridium* growth and toxinogenesis, it is safe to assume that continuous education and information to consumers on the best hygienic practices and on the correct home-canning procedures are the most effective preventive measures.

Adult intestinal colonisation botulism is very rare, both in Italy and worldwide. As reported by Fenicia and colleagues [20], abnormality of the gastrointestinal tract following inflammatory intestinal diseases or surgery, and alterations produced by broad-spectrum antibiotics in the endogenous microbiota, which act as the natural barrier to intestinal colonisation, are the only predisposing factor recognised to date. However, the patients from whom *C. butyricum* type E was recovered had Meckel's diverticulum, which may be considered as a possible predisposing factor for this form of botulism.

With respect to infant botulism, it is important to note that the relatively high number of cases reported in Italy are concentrated in a few paediatric hospitals in a few regions (Table 2), thanks to physicians who have acquired high awareness of this form of botulism and are able to promptly formulate clinical suspicion. Greater efforts have to be made to improve awareness among physicians operating in small-town hospitals. In fact, in many cases the diagnosis of infant botulism was formulated only once the patients were transferred from small, local hospitals to the paediatric hospitals mentioned above. Often the diagnosis of infant botulism is closely related to honey consumption, although other sources of contamination have also been identified [9].

Considerable efforts are needed to improve diagnostic skills in order to identify wound botulism in drug users. Indeed, diagnosis of this rare form of botulism is made more difficult by some drug effects, which can mask neurological symptoms at their onset. The incidence of only a single confirmed case is representative of the difficulties encountered by the physicians in the diagnosis of this form of botulism.

As revealed by the high number of laboratory-confirmed infant botulism cases in Italy, and by the low number of food-borne cases constituting outbreaks (mean cases per outbreaks = 1.5; range: 1–16 cases), the Italian botulism surveillance system demonstrates the ability to recognise and diagnose botulism and implement appropriate control procedures. A synergistic combination of epidemiological investigations and the ability of designated laboratories to detect the causative organism and transmission vehicles provides an effective way to tackle botulism emergencies. However, greater efforts must be put into reaching out to the public in order to increase awareness of food-borne botulism risks and promote correct home-preservation and canning practices. At the same time there is a need for increased awareness among front line medical professionals about the different forms of botulism so that clinical suspicion is considered early, which is essential for prompt diagnosis and treatment of patients.

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Conflict of interest

None declared.

Authors' contributions

Anniballi F and Auricchio B participated in study's design, data analysis, manuscript drafting and supervision of the study; Fiore A and Lonati D performed data collection and data analysis; Locatelli CA, Lista F, Fillo S contributed to the interpretation of data; Mandarino G and De Medici D contributed to manuscript drafting. All authors read and critically revised the manuscript drafts and approved the final version.

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Research article

The Maritime Declaration of Health (MDH) as a tool to detect maritime traffic-related health risks: analysis of MDH forms submitted to Spanish ports, October 2014 to March 2015

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The international maritime traffic of people and goods has often contributed to the spread of pathogens affecting public health. The Maritime Declaration of Health (MDH), according to the International Health Regulations (IHR) (2005), is a document containing data related to the state of health on board a ship during passage and on arrival at port. It is a useful tool for early detection of public health risks. The main objective of our study was to evaluate compliance with the model provided in the IHR, focusing on the format and degree of completion of MDH forms received at Spanish ports. We reviewed the content of 802 MDH forms submitted to nine Spanish ports between October 2014 and March 2015. Study results show that 22% of MDH forms presented did not comply with the recommended model and 39% were incomplete. The proportion of cargo ships with correct and complete MDH forms was lower than passenger ships; thus, the nine health questions were answered less frequently by cargo ships than passenger ships (63% vs 90%, p value < 0.001). The appropriate demand and usage of MDH forms by competent authorities should improve the quality of the document as a tool and improve risk assessment.

Introduction

In today's interdependent and interconnected world, it is possible for diseases to spread rapidly across the world and threaten public health. This is possible because of highly mobile human populations, international transport and trade. International public health security depends on the appropriate management of public health risks, which in turn depend on national capacities and international collaboration [1,2]. Effective public health measures and response capacities at airports, ports and ground crossings worldwide reduce the risk of the international spread of disease [3-5].

The International Health Regulations (IHR) (2005) [6] is a key international public health document that is legally binding across 196 countries, including all World Health Organization (WHO) Member States, requiring them to work together for global health security. This fundamental document requires that ratifying countries have the ability to detect, assess, report and respond to public health events [7,8].

The IHR (2005) includes provisions for the use of various health documents that can be presented, if requested, to health authorities on arrival at ports and airports [9]: the Ship Sanitation Certificate (Annex 3), the International Certificate of Vaccination and Prophylaxis (Annex 6), the Maritime Declaration of Health (MDH) (Annex 8) and the Health Part of the Aircraft General Declaration (Annex 9). If these

Table 1

Number of analysed Maritime Declaration of Health forms from different ports of call, Spain, October 2014 to March 2015 (n = 802)

The ports and their geographical area	Number of MDH forms (n)	Percentage of total (%)
Atlantic Ocean ports on the northern coast	**209**	**26**
A Coruña	101	13
Santander	27	3
Vigo	81	10
Atlantic Ocean ports on the southern coasts and the Canary Islands	**285**	**36**
Algeciras	93	12
Huelva	95	12
Santa Cruz de Tenerife	97	12
Mediterranean Sea ports	**308**	**38**
Barcelona	100	12
Tarragona	101	13
Málaga	107	13
Total number of MDH forms	**802**	**100**

MDH: Maritime Declaration of Health.

documents are used inappropriately, it may result in an inadequate assessment of public health issues related to international traffic. There is also an IHR List of Authorized Ports to Issue Ship Sanitation Certificates, published and updated by the WHO, that lists all ports each state party has authorised to issue Ship Sanitation Certificates [10]. According to Article 37 of the IHR (2005) [6], 'the master of a ship, before arrival at its first port of call in the territory of a State Party, shall ascertain the state of health on board, and, except when that State Party does not require it, the master shall, on arrival, or in advance of the vessel's arrival if the vessel is so equipped and the State Party requires such advance delivery, complete and deliver to the competent authority for that port a Maritime Declaration of Health which shall be countersigned by the ship's surgeon, if one is carried'. The state party may decide whether it requires all arriving ships to submit a MDH, which should conform to the model provided in Annex 8 of the IHR [6]. For European Union (EU) countries, according to Directive 2010/65/EU, the MDH is one of the forms that must be submitted to the first European port of arrival [11]. The EU SHIPSAN ACT Information System (SIS), developed within the scope of the EU SHIPSAN ACT Joint Action [12], allows port health authorities to confidentially share completed MDH forms between EU ports. Seamless and close communication between the master and port health authorities via the MDH enables the latter to detect on-board health problems that might constitute a risk to public health at an early stage and to take immediate measures to reduce the risk of onward transmission [13]. Therefore, it is essential that a MDH form is completed correctly at the onset of the assessment [13].

The International Maritime Organization (IMO) is a specialised agency of the United Nations that is responsible for measures to improve the safety and security of international shipping, and to prevent pollution from ships. One of its conventions, the Convention on Facilitation of International Maritime Traffic (FAL Convention), aims to facilitate maritime transport by simplifying and minimising formalities, data requirements and procedures associated with the arrival, stay and departure of ships engaged in international voyage [14]. The FAL Convention's main objectives are to 'prevent unnecessary delays in maritime traffic, to aid co-operation between Governments, and to secure the highest practicable degree of uniformity in formalities and other procedures. In particular, the Convention reduces the number of declarations which can be required by public authorities' [14]. At present, according to FAL Convention, ships may be required to complete nine documents: seven IMO-standardised forms (the General Declaration, Cargo Declaration, Ship's Stores Declaration, Crew's Effects Declaration, Crew List, Passenger List and Dangerous Goods Declaration), one Universal Postal Convention document and one International Health Regulations document (the MDH). Health authorities do not systematically inspect all ships, however, they review all the MDH presented.

Spain's geographical position, and the fact that it is a peninsula with 8,000 km of coastline with access to the Mediterranean Sea and the Atlantic Ocean, favour the frequent passage of ships [15]. As of 2016, Spain had 33 ports authorised to issue Ship Sanitation Certificates under the IHR [10]. All of these have medical inspectors (port health authorities) to evaluate events that suggest health risks on ships. For these reasons, and because there are numerous ports with high volumes of maritime traffic, cargo and passengers, Spain was considered ideal in terms of studying the quality of MDH forms.

Table 2

Proportion of passenger and cargo ships with properly filled Maritime Declaration of Health forms, Spain, October 2014 to March 2015 (n = 802)

Fields and questions in MDH forms	Properly filled (%)			p value
	Total ships (n = 802)	Cargo ships (n = 455)	Passenger ships (n = 347)	
Port of submission	95	92	98	0.004
Date of submission	95	92	99	< 0.001
Name of ship	99	99	99	0.925
Registration/IMO number	79	68	93	< 0.001
Arriving from	96	93	99	0.005
Sailing to	68	45	97	< 0.001
Nationality/flag of ship	96	97	95	0.048
Master's name	98	98	98	0.610
Gross tonnage	85	80	92	< 0.001
Valid Ship Sanitation Certificate	92	90	94	< 0.001
Place of issue	95	95	95	0.206
Date of Ship Sanitation Certificate	95	95	96	0.066
Re-inspection required	69	60	82	< 0.001
Has ship visited an affected area	71	60	86	< 0.001
Number of crew members on board	86	94	76	< 0.001
Number of passengers on board[a]	35	4	76	< 0.001
Completely filled nine health questions	75	63	90	< 0.001
Signed by the master	85	92	75	< 0.001
Signed by the ship's surgeon[a]	32	0.4	73	< 0.001
Date of signature	86	85	86	0.158
Presence of Attachment to Model of MDH[b]	10	2	22	< 0.001

IMO: International Maritime Organization; MDH: Maritime Declaration of Health.

[a] Generally only applicable to passenger ships.

[b] The presence of an Attachment to Model of MDH indicates that there is at least one case of illness on board the vessel. Thus, this field is only applicable to ships with positive MDHs (health problem(s) on board).

The aim of this study was to examine current MDH practice, as there are no previous studies on this issue, in order to enable health authorities to improve their capacity to detect and respond to health problems on board ships. For this purpose, we were mainly interested in evaluating whether the MDH forms used by ships conformed to the model set out in Annex 8 of IHR (2005), the extent of the form's completion by ships, and whether there were differences in completion and content depending on the type of ship or the geographical area of the port.

Methods

Study design

This was a descriptive study of MDH forms presented to Spanish ports by ships from all shipping routes. The object of analysis was the MDH form submitted by each ship to port authorities. The study analysed and compared MDH forms from different types of ships, as well as different MDH types.

Sample size

We calculated the representative sample size using the following information: in 2014 ca 140,000 ships arrived at Spanish ports [15]. First, we studied MDH forms presented to port authorities over a 6-month period, from October 2014 to March 2015. Then, based on an estimated population of 70,000 ships over a 6-month period, with a 99% confidence level and a 5% margin of error, the calculated minimum sample size was 569 MDH forms.

Participating ports

Nine of Spain's 33 IHR-authorised ports participated in this study: A Coruña, Santander and Vigo (Atlantic Ocean ports on the northern coast); Algeciras, Santa Cruz de Tenerife and Huelva (Atlantic Ocean ports on the southern coasts and Canary Islands); and Barcelona, Malaga and Tarragona (Mediterranean Sea ports). They were selected based on geography (to obtain information on the different shipping routes) and their inclusion on the IHR list of ports authorised to issue Ship Sanitation Certificates at the time of the study [10]. We requested 100 consecutive MDH forms

Table 3

Proportion of passenger and cargo ships with a Maritime Declaration of Health that conforms to the model provided in Annex 8 of the IHR (2005) and reports on existence of a valid Ship Sanitation Certificate, Spain, October 2014 to March 2015 (n = 802)

Maritime Declaration of Health form	Total ships (n=802)		Cargo ships (n=455)		Passenger ships (n=347)		p value
	n	Percentage of total (%)	n	Percentage of cargo (%)	n	Percentage of passenger (%)	
Conforms to the model MDH (Annex 8 of IHR 2005)	624	78	299	66	325	94	< 0.001
MDH reporting a Ship Sanitation Certificate issued by an authorised port[a]	690	86	371	81	319	92	< 0.001
MDH reporting a Ship Sanitation Certificate issued ≤6 months before date of MDH	716	89	384	84	332	96	< 0.001
MDH positive[b]	91	11	8	2	83	24	< 0.001

IHR: International Health Regulations; MDH: Maritime Declaration of Health.

[a] Port included in the IHR list of ports authorised to issue Ship Sanitation Certificates.

[b] MDH report on the presence of any health problem on board.

from each port from October 2014 onwards in the order in which they were presented at the port.

Questionnaire to study MDH forms

Questions and items on the model MDH form (Annex 8 of IHR 2005) include [6]: (i) questions regarding general ship information such as port and date of submission, name of ship, registration/IMO number, port of origin and destination, flag of ship, master's name, gross tonnage, port and date of issue of sanitation control certificate, inspection requirement, visit of affected areas identified by WHO (ports and date), and number of crew members and passengers on board; (ii) health-related questions regarding number of deaths on board due to illness, presence of infectious diseases on board during passage, frequency of ill crew and passengers, presence of ill persons at the time of MDH submission, medical consultation, presence of disease transmission risk factors, control measures taken, presence of stowaways on board, and presence of sick animals on board; (iii) signature of captain, signature of surgeon (if carried), and date of MDH . Finally, for each individual aboard the ship who is ill, the MDH is to be accompanied by a form called the Attachment to Model of MDH. This attachment requests information about the person's age, sex, nationality, date they joined the ship, nature of illness, date of symptom onset, etc.

Based on the model MDH form [6], we developed a questionnaire to assess the filling in completion and correctness of each field of the MDH forms used by the ships, which are based on but may differ from the model. The answers have been categorised into five options: (i) Yes, correct (field completed and correct); (ii) Yes, wrong (field completed but contains an error); (iii) Yes, unclear (field completed but illegible); (iv) No (field not completed); and (v) Not applicable.

Other questions included in the questionnaire concerned (i) the model of the MDH: based on the format shown in Annex 8 of the IHR (2005) or another format; (ii) the ship type: cargo ship or passenger ship; (iii) the port of submission: A Coruña, Santander, Vigo, Algeciras, Santa Cruz de Tenerife, Huelva, Barcelona, Málaga or Tarragona; (iv) the geographical location of the port: Mediterranean Sea coast, North Atlantic Ocean coast and South Atlantic Ocean coast (Table 1); (v) the 'type' of MDH: positive (health problem(s) on board) or negative (no health problem(s) on board); (vi) the validity of the Ship Sanitation Certificate: yes or no. Yes, if A. and B. below were correct; No, if A. or B. were not correct. A. Ship Sanitation Certificate issued by an authorised port i.e. one included in the IHR list of ports authorised to issue Ship Sanitation Certificates at the time of the study; and B. Ship Sanitation Certificate stated date of expedition less than or equal to 6 months according to Article 39 of the IHR (2005). This period may be extended by one month if the required inspection or control measures cannot be accomplished at the port.

To avoid inter-observer bias, all MDH forms were reviewed by a single observer. Any uncertainty of the single observer was resolved by the first four authors of the study via a specific procedure.

Data were entered and analysed using SPSS 15.0. We undertook descriptive statistics for each variable in the questionnaire. For those variables that could influence the distribution (e.g. type of ship, geographical area of the port and type of MDH (positive or negative), we used a chi-squared test to study the possible differences in the filling out of the questions on the MDH form in terms of completion and correctness. We studied the measures of association for nominal data: Pearson's contingency coefficient C, Cramer's V coefficient and phi coefficient. A value of $p<0.05$ was considered statistically significant.

Results

We analysed a total of 802 MDH forms submitted to nine selected ports. The ports and geographical areas where the MDH forms were submitted are shown in Table 1. Regarding these forms, 57% (n = 347) were submitted by passenger ships and 43% (n = 455) by cargo ships. Table 2 shows the proportion of each document field that was properly (completely and correctly filled), and the differences between cargo and passenger ships. We found that the nine health questions were properly answered in just 75% (n = 601) of the submitted MDH forms. The question asking whether the ship had visited an affected area was unanswered in 29% of MDH forms. In addition, 15% of the forms were not signed by the ship's master, which is required according to Article 37 of the IHR.

As shown in Table 3, the MDH form presented at the ports did not conform to the model provided in Annex 8 in 22% of 802 ships' MDH documents studied. In most cases, this is because a form following the model in an older Annex 8 of the IHR (2005) was submitted, for example, the model version from the IHR (1969). Furthermore, 86% of all ships had a Ship Sanitation Certificate issued from an IHR-authorised port and 89% of all ships had such certificates issued less or equal than 6 months before date of MDH. Of the 802 declarations surveyed, only 91 (11%) were positive (identifying a health problem on board); 83 from passenger ships and eight from cargo ships. Among those that were positive, seven did not fill out the Attachment to Model of MDH, which is required by the IHR (2005). Acute gastroenteritis, influenza or influenza-like illnesses, and measles were the most frequently reported health issues in the 91 positive MDH reports (45%, 10% and 10%, respectively).

Some variables, including ship type, geographical area of the port, and type of MDH, were studied regarding the degree of completion of the document and validity. We found statistically significant associations between the type of ship 'passenger' and the following variables: (i) greater probability that the items of the MDH will be complete (Table 2); (ii) the MDH model is consistent with Annex 8 of the IHR (2005) (Table 3); (iii) the Ship Sanitation Certificate was issued by an authorised port (Table 3); and (iv) the Ship Sanitation Certificate was issued less or equal than 6 months before date of MDH) (Table 3). The comparison of positive MDHs between cargo and passenger ships could not be carried out because of the low number of positive MDHs from cargo ships. Only five of the analysed variables showed significant differences when positive and negative MDH forms were compared:

- Ship type: only 2% (8/455) of cargo ships issued a positive MDH, while 24% (83/347) of passenger ships did so ($p=0.000$).

- Invalid Ship Sanitation Certificates because issued from a non-authorised port: 4% (4/91) of positive MDH forms and 15% (108/711) of negative forms ($p=0.005$).

- Invalid Ship Sanitation Certificates because more than 6 months between date of issue and date on the MDH form: 3% (3/91) of positive MDH forms and 12% (83/711) of negative forms ($p=0.015$).

- Missing the signature of the ship's master: 32% (29/91) of positive MDH forms and 10% (72/711) of negative forms ($p<0.001$).

- Missing the next port of destination: 13% (93/711) of the negative MDH forms and 3% (3/91) of positive forms ($p<0.000$).

When comparing the MDH variables between different geographical areas we found some statistically significant differences. However, these differences disappear if the variable 'type of ship' is introduced in the analysis. Cargo ships are most frequently in the ports on the Atlantic Ocean coast (64% cargo ships vs 36% passenger ships) and passenger ships are most frequently in the ports on the Mediterranean Sea coast (55% passenger vs 45% cargo) ($p < 0.001$).

Discussion

There are a few studies to date that analyse compliance with the IHR (2005) recommendations and the use of related documents. In 2011, Hadjichristodoulou et al. [9] reported that the MDH was the main reporting tool used for the surveillance and monitoring of communicable diseases on passenger ships in Europe. However, only 30% of the 59 competent authorities surveyed reported that they require all arriving ships to submit MDH forms. In special situations of health surveillance, as in during the early stages of pandemic influenza A in 2009, Schlaich et al. [16] showed that 32% of shipping companies experienced one or more health screening measures by port health authorities. Furthermore, a request to complete the MDH form was reported by 23% of the companies that participated in the study (7/31).

As of 2016, 115 of 171 IMO members have acceded to the FAL Convention [14]. The FAL Convention and Directive 2010/65/EU of the European Parliament and of the Council have included the MDH document among the nine documents that all ships must electronically submit (promptly and correctly filled out) if requested to do so by port authorities [11,14]. Furthermore, several studies recommend greater and better use of the MDH as modelled in Annex 8 of the IHR (2005) [17-19]. Our results show that a high proportion of the MDH forms submitted did not conform to the 2005 model (22%), have incomplete information on relevant data (only 75% completed the nine health questions) or have invalid Ship Sanitation Certificates (ca 1 in 5 cargo ships and 1 in 10 passenger ships) because the date of issue was ≥ 6 months and/or the port was not authorised. The communication of any condition on board a ship (gastrointestinal illness, haemorrhagic fevers, respiratory diseases, etc.) to port health authorities via the MDH form provides the opportunity for more efficient responses, including making a faster diagnosis, disembarking patients, identifying contacts and facilitating the adoption of health measures [20]. An incomplete MDH makes it difficult to assess risks and requires additional communication with the ship to obtain the missing information. Such omissions lengthen the response time, and reduce the effectiveness and efficiency of monitoring. This highlights the importance of fully completing the MDH form for the early detection of events and for timely implementation of public health measures on board ships, as per the WHO requirements [3].

Cargo ships require greater attention by the port health authorities as our study shows that their MDH forms are more frequently incomplete. Unlike passenger ships, freighters often lack medical services, make longer journeys and use multiple shipping routes, which can hinder the management of diseases.

Usually, when a correct and complete MDH informs the port health authorities of communicable diseases or other potential public health problems, competent authorities assess the information, confirm the situation on board and propose appropriate measures for each situation, such as isolation, landing, disinfestation, decontamination and vaccination.

It should be considered as a limitation that this study was unable to determine if all ships with potential health risks on board recorded this information on a MDH form because health authorities do not systematically inspect all ships. In addition, given that descriptive studies often represent the first scientific dip into new areas of inquiry, the limitations of this study must be addressed in subsequent analytical studies [21]. Further studies are required to assess whether the MDH is, in practice, a reliable reporting tool. For this, it would be necessary to inspect all ships arriving at ports, interview masters or doctors on board, and check whether the information recorded on MDH forms represents the reality on board; however, this is not a feasible goal.

Conclusions and recommendations

The MDH document brings together information to assess the state of health on board a ship. Its proper completion is key to conducting a preliminary risk assessment, and efforts should be made to achieve this goal. Thus, masters and specific crew members should be properly trained to complete the MDH in such a way that port health authorities can assess the situation in advance.

We believe that an improvement in the current use of the MDH will result in improved risk assessment, greater confidence in the information provided and improve the trust between ships, health authorities and other stakeholders in the port, such as conveyance operators, relevant port authorities and surveillance system operators. Monitoring the implementation of the IHR (2005) guidelines related to the MDH should not only include monitoring the use of appropriate communication channels, but also an evaluation of the quality of the information provided. In later phases, the proper use of the MDH should be assessed and measured to prevent and provide a public health response to the international spread of disease.

Several countries might be involved in the response to an outbreak on board a ship. Therefore, the MDH should not be considered an isolated document concerning only one country, but a source of information that should be shared between port health authorities for follow-up action. The use of the SIS, a tool developed by the EU SHIPSAN project for the immediate sharing of information between ports, should be encouraged for the transmission of such information. Further, training masters on the importance of the MDH and how to routinely use it would also help facilitate prompt responses in the case of a complex public health event occurring on their ships.

Finally, further studies should be conducted to assess the real value of the MDH as a public health assessment tool for events on ships. One such avenue could be the analysis of the consequences to public health when the MDH is not properly completed.

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Conflict of interest

None declared.

Authors' contributions

All authors have contributed directly to the intellectual content of the paper. Particular contributions are as follows: RM López-Gigosos, M Segura, RM Díez-Díaz, I.Ureña and M. Dávila have developed the concept of the manuscript, have managed the database, analysed the data and have wrote the first draft. D.Urzay, P.Guilloy, A.Guerra-Neira, A.Ribera, A.Perez-Cobaleda, A.Martín., M.Nuñez-Torrón, B. Alvarez, M. Faraco, JM Barrera, MJ Calvo, J. Gallegos, A. Bermejo, and C. Aramburu, contributed to the study with data from their respective ports, analysis of data and, provided comments on the final manuscript. M. Dávila., F. Carreras, and R. Neipp have been involved in the planning and design of the scheme, have participated in the analysis and interpretation the results critically and have revised the article for important content. A. Mariscal provided epidemiological expertise, and also has made a substantial contribution to final revision.

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