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Short communication

Hepatitis A—2017 an unusual year in Scotland

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ABSTRACT

Background: The number of cases of acute hepatitis A reported in Scotland each year is small, and the majority of cases have been associated with travel to endemic regions. However, in early 2017, in the midst of ongoing outbreaks of hepatitis A among MSM in Europe, there was a sharp rise in the number of cases reported to Health Protection Scotland.

Objectives: The initial aim of this study was to investigate the reason for the observed increase in cases of hepatitis A at the start of 2017. As cases continued for the remainder of the year, these cases were typed to determine whether these cases were linked to each other, or other outbreaks.

Study design: The study population consisted of 42 hepatitis A infected patients with no obvious source of infection. The patient samples were collected between January and December 2017. The VP1/2 A region was amplified and sequenced.

Results: The majority of samples typed as genotype 1 A (n = 17) or genotype 1B (n = 15). Within genotype 1 A, fifteen samples had strains (VRD_521_2016 or RIVM_HAV16_090) associated with ongoing outbreaks of hepatitis A in MSM in Europe. Within genotype 1B, there were four clusters of infections, with identical cases in geographically distinct regions with no identified epidemiological link.

Conclusions: Molecular typing proved useful, as it allowed public health to identify clusters, establish links with other outbreaks and compare Scottish strains with those reported elsewhere.

1. Background

Hepatitis A is a vaccine-preventable infection that mostly causes a mild or asymptomatic infection in children with severity generally increasing with age [1,2]. The virus is endemic in the developing world and is transmitted predominantly via the faecal-oral route or via contaminated food or drink. In the United Kingdom, individuals most at risk of acquiring Hepatitis A virus (HAV) are those travelling to endemic regions, men who have sex with men (MSM) and people who inject drugs [3]. In recent years there have also been a number of international foodborne outbreaks associated with a range of foods imported from endemic regions, including berries, semidried tomatoes, and seafood [5–8]. Most recently there has been a large international outbreak affecting mostly MSM which occurred throughout Europe since June 2016 [4]. Six HAV genotypes have been described based on sequence variation in the VP1/2 A region [9]. Only genotypes I-III, divided into subgenotypes A and B, have been described in humans. Sequencing has enabled early detection of outbreaks, identified cases with no epidemiological link, provided confirmation of the contaminated food source, and established links between outbreaks in multiple countries [5,6,8].

In Scotland, Hepatitis A is a notifiable disease with all cases reported to Health Protection Scotland (HPS). However, at present, cases are not routinely sequenced. Since 2006, the number of cases of acute HAV in Scotland has remained steady at around 29 cases per year (range 18 to 48). In early 2017, HPS noticed an increase in the number of cases of HAV across Scotland, with 26 new cases by week 13. As the majority of these cases did not have any obvious risk factors for acquiring HAV, and were from multiple health boards, a national problem assessment group was established [10].

2. Objectives

As part of the initial investigation, the West of Scotland Specialist Virology Centre (WOSSVC) sequenced all cases of HAV from January to April 2017. WOSSVC continued to sequence any cases with no obvious

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source for the remainder of 2017. This was to determine whether these cases were linked microbiologically to each other and/or outbreaks outside Scotland.

3. Study design

3.1. Molecular analysis

From January to December 2017, there were 153 cases of Hepatitis A reported to HPS. This included 91 cases associated with a large outbreak of food-related Hepatitis A which occurred in Lanarkshire during April 2017. The present report does not cover this outbreak. Plasma or serum samples from 42 of the remaining 62 patients were referred to the WOSSVC for HAV sequencing. The VP1/2 A region (396 nt) was amplified and sequenced using primers previously described [11]. All nucleotide sequences were compared with reference HAV sequences that included each of the three MSM outbreak strains using MEGA (6.0) software [12]. HAV sequences were submitted to the HAVNET database

4. Results

4.1. Patient demographics

Overall, there were 62 cases of laboratory confirmed Hepatitis A reported to HPS between January and December 2017 (excluding the 91 cases associated with a food-borne outbreak in Lanarkshire), which was a substantial increase on previous years (Fig. 1). The majority of HAV cases were male (75%), this compares to a yearly average of 49.3% between 2011 and 2016 (range 27.8%–72.2%). The median age was 45 years (range < 5 to > 80 years).

4.2. Hepatitis A typing

The VP1/2 A region was successfully amplified and sequenced in 34/42 patient samples. Eight samples failed to amplify as they were PCR negative at the time of sample collection. Phylogenetic analysis revealed that the majority of samples typed as genotype 1 A (n = 17) or genotype 1B (n = 15) (Fig. 2). Two patient sequences were genotype 3 A. Genotype 3 A is similar to strains found in Pakistan, which is in keeping with the travel history for one of these patients. The second genotype 3 A patient had no history of recent travel.

Within genotype 1 A, fifteen patients had strains associated with ongoing outbreaks of HAV in MSM in Europe; nine had strain VRD_521_2016 and six had strain RIVM_HAV16_090 (Table 1) [4]. These patients were located across Scotland. The majority (13/15)

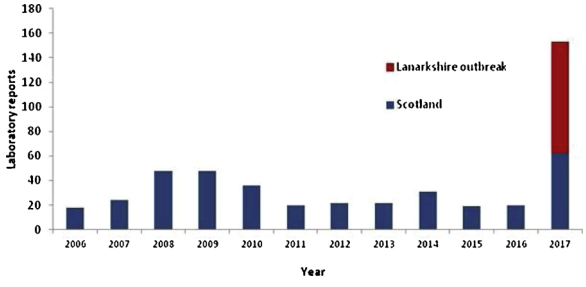

Fig. 1. Laboratory confirmed cases of Hepatitis A in Scotland by year (2006–2017).

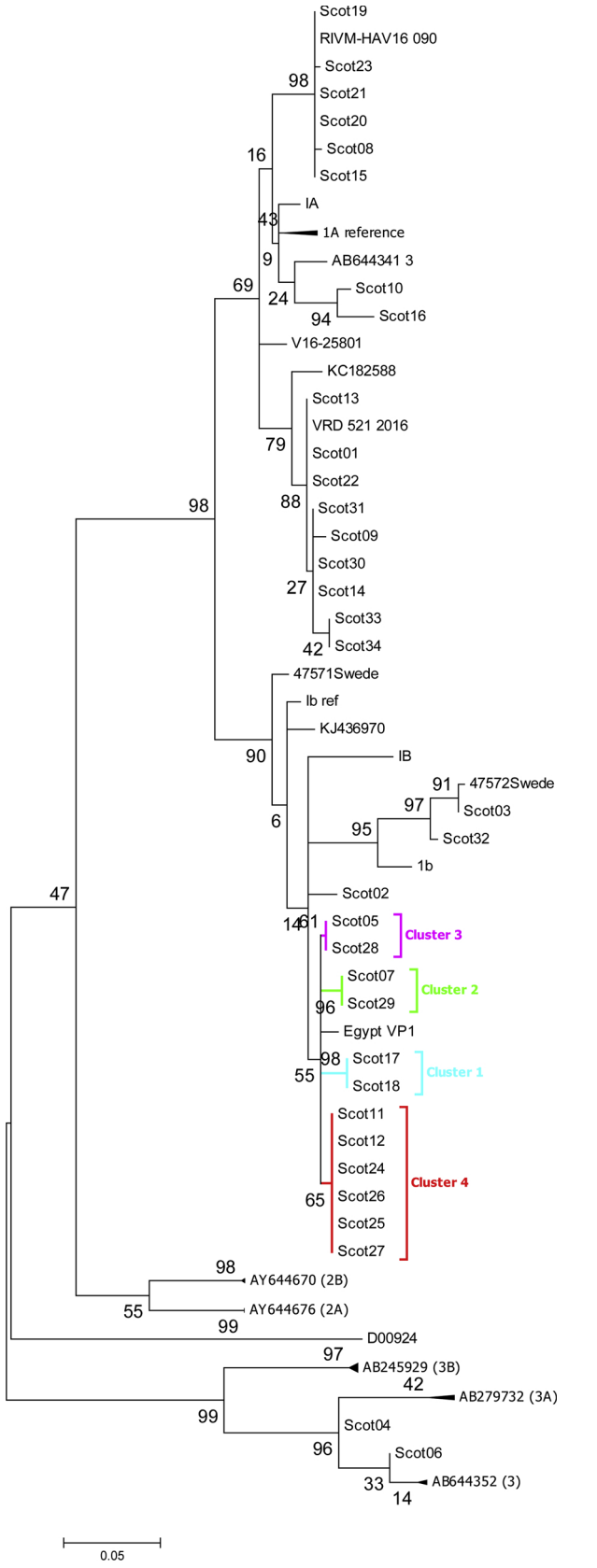

Fig. 2. Maximum Likelihood Phylogenetic tree of Scottish Hepatitis A VP1/2 A sequences A distance-based maximum likelihood phylogenetic tree with bootstrap analysis (1000 replicates) was generated using MEGA 6.0 software. All Scottish sequences have been anonymised (Scot1-Scot32). Reference sequences from Genbank and HAVNET databases have been included for comparison.

Table 1
Distribution of Hepatitis A genotypes in Scotland in 2017.

HAV genotype	Number of cases
VRD_521_2016 (G1 A)*	9
RIVM-HAV16-090 (G1 A)*	6
G1 A	2
G1B (8 subtypes)	15
GIIIA	1
GIIIB	1
Total	34

* These strains are associated with outbreaks of Hepatitis A that occurred in MSM across Europe during 2016/2017.

were men and some (6/10 for whom we have epidemiological information) identified themselves as MSM. Most cases were primary infections with a small number of transmissions within households (2/15).

The fifteen genotype 1B sequences fell into four clusters spread across four different health boards (Fig. 2, Table 2). Genotype 1B sequences are highly similar to strains found in Pakistan and Egypt. No common exposure source was identified for any of the primary cases in the clusters, although many reported consuming fresh or frozen berries from multiple suppliers.

5. Discussion

Historically, Hepatitis A in Scotland has been associated with travel to endemic regions with a small number of cases reported each year. However, in early 2017, in the midst of ongoing outbreaks of hepatitis A among MSM in Europe, there was a sharp rise in the number of cases reported to HPS [4]. As a consequence, confirmed cases of HAV, with no obvious source, were sequenced throughout 2017. Thirty four patient samples were sequenced, the majority of which were genotype 1 (n = 32) which is the most prevalent genotype worldwide [6]. Among those sequenced, 44% belong to sequence types associated with MSM clusters (Table 1).

The increased incidence reported in Scotland in 2017 was similar to that reported by Public Health England (PHE) for England and Wales, which saw an increase of 112% compared to 2016 [13]. The proportion of cases with genotype 1 A infection in England and Wales was considerably higher (82.8%) than in Scotland, where 50% of cases were genotype 1 A. The low levels of diagnosed infection in MSM in Scotland likely reflects, in part, higher rates of HAV immunisation among the MSM community in Scotland prior to the outbreak, as many sexual health clinics offered either HAV vaccine alone or a combined HAV/Hepatitis B virus vaccine. In July 2017 there was a change in policy which led to the implementation of an HAV vaccination programme specifically targeted at the MSM community, this was part of the UK response to the outbreak and will have contributed to the subsequent decline in the number of cases of these strains across the UK [13,14].

The majority of the remaining Scottish patient samples (44%) were genotype 1B, most were identified in the first quarter of the year, and fell into four separate clusters. This is in contrast to numbers reported by PHE, where only 8.6% of samples were genotype 1B. This is likely reflecting the higher proportion of samples associated with the MSM outbreaks. Three of these genotype 1B clusters included patients from different health boards with identical or highly similar sequences. However, public health teams were unable to establish any epidemiological links. Despite the use of extended questionnaires, no common food or other source was identified, although many cases reported consumption of fresh and/or frozen berries, albeit from multiple sources. It is possible that these cases within clusters were linked due to contamination of food by infected food handlers at the source of the fruit picking [15], however in smaller clusters such as these, the food source is often never identified [13,16,17]. Only two patient samples were genotype 3 and one had a travel history consistent with the genotype identified. The source for the second genotype 3 patient was not identified.

Our experience during 2017 has demonstrated the value of molecular typing, as it allowed public health to; identify clusters, establish links with other outbreaks and compare Scottish strains with those reported elsewhere. Despite extensive investigations it wasn't possible to find a source of any of the four small clusters detected in the early part of 2017, however it was hypothesised this could be due to low level contamination of imported food during harvesting or packing prior to export.

Members of the problem assessment group

G Hawkins (HPS), A Smith-Palmer (HPS), Amanda Bradley Stewart (WoSSVC), Kate Mark (NHS Lothian), Maria Rossi (NHS Grampian), Emanuel Okpo (NHS Grampian) Colin Sumpter (NHS Forth Valley), Catriona Milosevic (NHS Greater Glasgow and Clyde), Jacqui Shookhye-Dickson (NHS Greater Glasgow and Clyde), Hilda Cruikshank (NHS Greater Glasgow and Clyde), Chris McGuigan (NHS Fife) Faiza Hansraj (HPS), Allan Shand (Food Standards Scotland), Kazia Kazimierczak (Food Standards Scotland), Ryan Bruce (Food Standards Scotland), Laura Lafferty (Food Standards Scotland), Kate Templeton (NHS Lothian), Rory Gunson (WoSSVC), Sarah Joselyn (Fife Council), Lorna Starkey (Fife Council).

Table 2
Scottish Hepatitis A genotype 1B clusters.

	Cluster 1	Cluster 2	Cluster 3	Cluster 4
Strain	G1B Scot17, Scot18	G1B Scot07, Scot29	G1B Scot05, Scot28	G1B Scot11, Scot12, Scot24-27
Multi or single health board	Single	Multi	Multi	Multi
Number of laboratory confirmed cases	2	2	2	8 (2 cases failed to sequence)
Primary / secondary	1 primary 1 secondary	2 primary	2 primary	4 primary 4 Secondary
Known risk factors	None identified	None identified	None identified	None identified

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Competing interests

None declared.

Ethical approval

Not required.

CRediT authorship contribution statement

Amanda Bradley-Stewart: Conceptualization, Methodology, Investigation, Data curation, Writing - original draft, Visualization, Formal analysis, Writing - review & editing. **Alison Smith-Palmer:** Methodology, Investigation, Data curation, Writing - review & editing. **Gill Hawkins:** Writing - review & editing. **Rory Gunson:** Conceptualization, Supervision, Writing - review & editing.

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