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Hepatitis A in Switzerland: An analysis of 29 years of surveillance data and contemporary challenges

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ABSTRACT

Background: Hepatitis A (HA) incidence declined in most European countries in the past decades. We analysed HA notification data for Switzerland of 29 years looking for disease- and notification system-related factors possibly contributing to observed trends.

Method: Notification data were descriptively analysed using five time intervals (1988–1993, 1994–1999, 2000–2005, 2006–2011, 2012–2016); and notification rates were calculated.

Results: From 1988 to 2016, the HA notification rate decreased from 9.5 to 0.5 per 100′000 population in Switzerland. Median age and the proportion of hospitalised cases increased over time. In the 1988–1993-time period, intravenous drug use was the most frequently mentioned risk exposure while consumption of contaminated food/beverages was most frequently mentioned in the 2012–2016-time period.

Conclusions: Notification data does not allow reliably identifying current risk groups (e.g. travellers) due to low case numbers, limited availability and reliability of information. It is important to document changes in the surveillance system for later analyses and interpretation of long-term trends. Population susceptibility likely increases underlining the importance of continued and continuous surveillance and prevention efforts despite decreasing case numbers. Operational research is recommended to further investigate observed trends of HA and to enhance the abilities for decision making from Swiss HA surveillance data.

1. Introduction

In most European countries, incidence and endemicity of hepatitis A virus (HAV) infection are classified as low or very low[1] [2–5]. However, this does not mean that the disease can be ignored. It rather implies that the characteristics of HAV infections differ from those countries with high or intermediate HAV endemicity features.

HAV infection is usually asymptomatic or mild in young children [6]. HAV infection is more often symptomatic with increasing age, and may present with fever, malaise, anorexia, nausea, abdominal discomfort, diarrhoea, vomiting, fatigue and jaundice after an incubation period of 15–50 days [1,6]. Signs and symptoms of acute hepatitis A (HA) are indistinguishable from acute hepatitis B (HBV) and C virus (HCV) infections [6]. However, in contrast to HBV and HCV, HAV does not lead to chronic infection even though relapse of symptoms and fulminant hepatitis can occur [6].

Safe and effective vaccines against HAV exist. HAV vaccination rather than passive immunisation is recommended for pre- and post-exposure prophylaxis and can be considered to contain outbreaks [1]. In areas of high endemicity, most people get infected at very young age. Hence, asymptomatic infection is likely and the burden of disease of HA is low in these countries. With decreasing level of endemicity, average age at infection and disease severity increase. Therefore, it is assumed that countries with intermediate endemicity levels benefit the most from universal vaccination against HAV [1]. The World Health Organization (WHO) recommends large-scale vaccination in areas with intermediate HAV endemicity and targeted vaccination of people at high risk in areas of low and very low endemicity [1].

HAV is transmitted via the faecal-oral route from person-to-person or through contaminated food and water [6]. Young children are an important reservoir and source of transmission considering that the majority of young children infected with HAV are asymptomatic [6,7].

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[1] Levels of endemicity have been defined by WHO on the basis of seroprevalence as follows: “high (≥90% by age 10 years); intermediate (≥50% by age 15 years, with < 90% by age 10 years); low (≥50% by age 30 years, with < 50% by age 15); and very low (< 50% by age 30 years)” [1].

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Abbreviations

CI	confidence interval
ECDC	European Centres for Disease Prevention and Control
EEA	European Economic Area
EU	European Union
FOPH	Federal Office of Public Health
FSO	Federal Statistical Office
HA	Hepatitis A
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICD-10	International Classification of Diseases and Related Health Problems 10th revision
IDU	Injecting drug user
MSM	Men who have sex with men
NNSID	National Notification System for Infectious Diseases
VFR	[travellers] visiting friends and relatives
WHO	World Health Organization

Infectivity of HA is highest during the second half of the incubation period up until a few days after onset of jaundice [6]. Most people are no longer infectious one week after onset of jaundice [6]. High-risk groups for HAV infection include unimmunised travellers to areas of high endemicity, men who have sex with men (MSM), and injecting drug users (IDUs) [1].

Case fatality of HA ranges from 0.1 to 0.3%, but increases strongly with age with rates of sometimes > 10% observed in hospitalised adults ≥40 year old or older age groups [6,8,9]. Globally, 14′900 deaths were attributable to HAV infection in 2013 compared to 22′600 in 1990 [10].

In 2016, WHO published a guide for viral hepatitis surveillance [11]. One of the three mentioned purposes of viral hepatitis surveillance is relevant for HA: “detect outbreaks, monitor trends in incidence and identify risk factors for new, incident infections”. Syndromic surveillance is recommended to detect outbreaks while enhanced case reporting is recommended to “describe trends in type-specific acute hepatitis and identify risk factors”. Case definitions suggested by WHO and case definitions used by the European Centres for Disease Prevention and Control (ECDC) and by the Federal Office of Public Health (FOPH) for Switzerland are presented in Table 1. In Switzerland, there is currently no syndromic surveillance for hepatitis but reporting of laboratory-confirmed cases of hepatitis A (and B and C; and hepatitis E as per 01.01.2018) is mandatory [12].

HAV seroprevalence and incidence vary substantially across countries of the European Union (EU) and the European Economic Area (EEA), but decreased in all countries between 1975 and 2014 [2,5]. However, the notification rate of HAV, 3.0 cases per 100′000 population in 2014, has been slightly increasing again since 2011 [13]. There is a high variability across EU/EEA countries also in terms of notification rates: Iceland reported zero cases per 100′000 population, while Romania reported 33.3 cases per 100′000 population in 2014. In Switzerland, the notification rate decreased from 10/100′000 population in 1988 to 2.6/100′000 population in 2004 [14].

Most EU/EEA countries recommend vaccination against HAV for selected risk groups while only few recommend universal vaccination (included in national immunisation programme: Greece; universal childhood vaccination for parts of the country: Italy, Spain; recommended, but not included in national immunisation schedule: Bulgaria, Cyprus, Czech Republic, Estonia) [2]. In Switzerland, the first HAV vaccine was available in 1992 [15]. Before, only passive immunisation was available for travellers at risk [15]. Risk groups, for which vaccination against HAV is recommended, are presented in Table 2. The costs of HAV vaccination have been covered by the compulsory health insurance for risk groups since 2008 except for travel-related and occupational indications [17]. For the latter, the employer usually covers the costs for vaccination.

This study describes the notification data of HA for Switzerland. It identifies factors potentially contributing to observed trends, including changes in the notification system. We investigated the epidemiology of HA in Switzerland in relation to the current Swiss vaccination recommendations and trends observed in other European countries.

2. Material and methods

2.1. The National Notification System for Infectious Diseases

HA has been a notifiable disease in Switzerland since 1984 [14]. Mandatory notification of HA includes a “report on laboratory findings” and a “report on clinical findings”. Current reporting forms can be accessed at www.bag.admin.ch/infreporting (available in German, French and Italian).

Reports on laboratory findings are completed by those responsible at the diagnosing laboratory, upon confirmation of a HAV infection. Reports are sent within 24 h to the FOPH and to the cantonal physician of the patient's canton of residence. The current laboratory notification form includes date of diagnosis, type of sample, laboratory method, patient's name, address, date of birth, and sex.

Physicians are to complete the “report on clinical findings” upon receipt of a positive laboratory result for HAV, and send it to the cantonal physician of the patient's canton of residence, within 24 h. The cantonal physician forwards this information to the FOPH and takes appropriate disease control and prevention measures, if indicated. The FOPH takes on and/or coordinates prevention and control measures if several cantons and/or other countries are involved, or if requested by the cantonal physician. The notification form on clinical findings contains information on the patient (name, date of birth, sex, address, nationality), and the course of disease (date of disease onset and diagnosis, signs and symptoms, reason for laboratory testing, hospitalisation, sequelae, death). The patient's vaccination status and exposure within 2 months before disease onset are also recorded. Information from both notification forms (laboratory and clinical findings) is then entered into an electronic database at the FOPH. Reports on the same patient are linked, whenever possible.

2.2. Data sources and analysis

Surveillance data on HA was extracted from the National Notification System for Infectious Diseases' (NNSID) database for the years 1988–2016 (data as of 12 April 2017). Data before 1988 were not available. Cases residing outside Switzerland and the Principality of Liechtenstein, and cases finally classified as “no case” (see Table 1 for case classification) were excluded.

Data were analysed descriptively in terms of case numbers and case characteristics (incl. possible transmission routes). For description of case characteristics, notification years were grouped into four 6-year- and one 5-year-period. Notification rates, defined as the number of notified cases per 100′000 resident population, were calculated using population statistics from the Federal Statistical Office (FSO). Population statistics were not yet available for 2016 at the time of data extraction; therefore, we used 2015 population statistics to calculate notification rates for 2016. We compared the number of hospitalised cases and deaths as reported on notification forms with the number of hospitalisations and deaths due to the International Classification of Diseases and Related Health Problems 10th revision (ICD-10) codes

B15.0 ("hepatitis A with hepatic coma") or B15.9 ("hepatitis A without hepatic coma") according to official hospital and mortality statistics (data obtained from the FSO). Main and secondary diagnoses/deaths were considered for extraction of hospitalisations/deaths due to ICD-10 codes B15.0 and B15.9 from hospital and mortality statistics, respectively. Data were analysed using the statistical software Stata (Version 13.1 [18]).

Notification data were collected under the Swiss Epidemics Act and hence, no ethical approval was required.

3. Results

3.1. Trends in hepatitis A case numbers and demographic characteristics

The notification rate of HA decreased from 9.5/100′000 population (628 cases) in 1988 to 0.5/100′000 population (43 cases) in 2016 in Switzerland (Fig. 1). The highest notification rate was observed in 1990 (14.2/100′000).

Median age of cases increased from 25 years (1988–1993) to 43 years (2012–2016). In the most recent years, no age group predominated while in the early 1990s there was a clear predominance of young adults for both sexes (highest notification rate in 15–24 year age

Table 1
World Health Organization (WHO), European Centre for Disease Prevention and Control (ECDC) and Federal Office of Public Health (FOPH) case definitions for hepatitis A surveillance.

Acute hepatitis/Hepatitis A case definition according to WHO [11]	
Presumptive case/case definition for syndromic surveillance ("acute hepatitis"):	Any person meeting the - **Clinical criteria**
Confirmed case (type-specific surveillance; hepatitis A):	Any person meeting the - **Clinical criteria** AND - **biomarker or epidemiological criteria** **Clinical criteria:** "Discrete onset of an acute illness with signs/symptoms of (i) acute viral illness (e.g. fever, malaise, fatigue) and (ii) liver damage, which can be clinical (e.g. anorexia, nausea, jaundice, dark urine, right upper quadrant tenderness), and/or biochemical (alanine aminotransferase [ALT] levels more than 10 times the upper limit of normal.[a]" [11] [a] Ten times the upper limit of normal (400 IU/L) is the threshold used by the State and Territorial Epidemiologists (CSTE). Countries may also select lower thresholds that could be more sensitive or higher thresholds that could be more specific **Biomarker criteria:** IgM anti-HAV positive **Epidemiological criteria:** Epidemiological link[b] with a confirmed case [11] [b] Contact with a confirmed case-patient during the referent exposure period or context of an etiologically confirmed outbreak
Hepatitis A case definition according to ECDC [70]	
Confirmed case	Any person meeting the - **Clinical criteria** AND - **Laboratory criteria**
Probable case	Any person meeting the - **Clinical criteria** AND - **Epidemiological criteria** **Clinical criteria:** "Any person with a discrete onset of symptoms (e.g. fatigue, abdominal pain, loss of appetite, intermittent nausea and vomiting) AND at least one of the following three: fever, jaundice, elevated serum aminotransferase levels" [70] **Laboratory criteria:** "At least one of the following three: detection of hepatitis A virus nucleic acid in serum or stool, hepatitis A virus specific antibody response, detection of hepatitis A virus antigen in stool" [70] **Epidemiological criteria:** "At least one of the following four: human to human transmission, exposure to a common source, exposure to contaminated food/drinking water, environmental exposure" [70]
Hepatitis A case definition according to FOPH	
Confirmed case	Any person meeting the - **Laboratory criteria** AND - **Clinical criteria** or **epidemiological link** In absence of information on laboratory criteria: - Both **clinical criteria** (icterus and increased transaminase) present AND **contact with laboratory-confirmed case**
Probable case	Any person meeting the - **Clinical criteria** but **without any information on laboratory criteria** (with indication of name of laboratory and/or reason for testing on clinical notification form)
Possible case	Any person meeting the - **Laboratory criteria** but **without any information on clinical and epidemiological criteria** OR - **Clinical criteria** but **without any information on laboratory criteria** (without indication of name of laboratory and/or reason for testing on clinical notification form)
No case	- **Neither laboratory nor clinical criteria met** OR - **Laboratory criteria** met, but **neither clinical criteria** met **nor epidemiological link** present (but information from clinical notification form is available) - **Neither laboratory criteria** met **nor epidemiological link** present (independent of presence or absence of clinical criteria) **Laboratory criteria:** anti-HAV IgM positive **Clinical criteria:** Icterus and/or increased transaminase **Epidemiological link:** Stay in an endemic region (high or moderate risk according to WHO, p. 95 [71]) or contact to a laboratory-confirmed case

Table 2
Overview of Swiss recommendations for vaccination against hepatitis A virus (HAV).

1992	2005	2007	Summary of current (2007) vaccination recommendations as published in yearly vaccination schedule (2017)
Source: [15]	Source: [16]	Source: [14]	Source: [17]
Primary prevention			
Non-immune travellers to countries with high risk of HAV infection (mainly "third world countries" and selected countries in Eastern Europe)	[travellers][a]	Travellers to countries with medium or high endemicity (according to www.who.int/ith or www.safetravel.ch). In case of adoption of a child from a country of high endemicity, all family members (not only those travelling) should be vaccinated	Travellers to countries with medium and high endemicity
Illegal drug users	Drug users	People injecting drugs	People injecting drugs
Partly recommended: Children > 12 months of age visiting relatives in "third world countries" or in Eastern Europe and attending day care in Switzerland		Children from countries of medium and high endemicity living in Switzerland and temporarily returning to their country of origin	Children from countries of medium and high endemicity living in Switzerland and temporarily returning to their country of origin
Partly recommended: Selected staff of day care facilities and children hospitals			
Partly recommended: Persons in close occupational contact with refugees, asylum seekers or drug users		Persons in close occupational contact to people injecting drugs (including prison staff); and to persons from countries of medium and high endemicity (asylum seekers, refugees)	Persons in close occupational contact to drug users; and to persons from countries of high endemicity
	Persons with chronic hepatopathies	Persons with chronic liver disease (Hepatitis B, C or other chronic hepatopathies, especially candidates of liver transplantation	Persons with chronic liver disease
	Persons in close contact to people with HAV infection		
	Staff of microbiological laboratories	Laboratory personnel working with HAV or with primates infected with HAV, or investigating stool samples	Laboratory personnel working with HAV
	Men who have sex with men (MSM)	Men who have sex with men (MSM) (outside of stable relationship)	Men who have sex with men (MSM)
		Drainers and employees of sewage plants	Drainers and employees of sewage plants
Secondary prevention			
		After close contact with a person with acute hepatitis A, or after exposure to a potential source within 7 days after exposure (or after development of symptoms of the primary case) Staff and persons in institutions, in which there was a case of HAV (e.g. day-care centres, home for persons with disabilities, retirement homes, casern), and their families, if appropriate In case of an epidemic (social environment of cases)	Within 7 days after exposure.

[a] Travel-related vaccination recommendations/indications were not considered in this document.

group, followed by 25–44 year age group; Fig. 2). In the two youngest and in the oldest age groups (0–4, 5–14 and 65 + age groups) there was no clear sex-pattern observed. In the 15–24, 25–44 and 45–65 year age groups, males had a higher notification rate. However, this male predominance decreased over the years. In 2015 and 2016, the overall female notification rate was even slightly higher than the male notification rate.

The proportion of cases of Swiss or Liechtensteiner nationality decreased during the observation period: 83.9% were Swiss/Liechtensteiner (excluding those with nationality not specified) during the 1988–1993-period, while in the 2012–2016-period 70.1% were reported to be Swiss/Liechtensteiner (Table 3). A similar trend was observed in the proportion of Swiss among the permanent resident population of Switzerland: in the 1988–1993-period, between 81.7 and 84.6% were of Swiss nationality while in the 2012–2015-period (2016 data not yet available) between 75.6 and 77.0% were Swiss [19].

In all notification periods, between 2.4 and 4.9% of cases were reported to be vaccinated against HAV. For 45 of 285 cases with reported vaccination prior to HA infection, at least the year of the first and/or last vaccination was reported. Of those, 3 were reported to be vaccinated before 1992, 13 received vaccination ≤14 days before disease

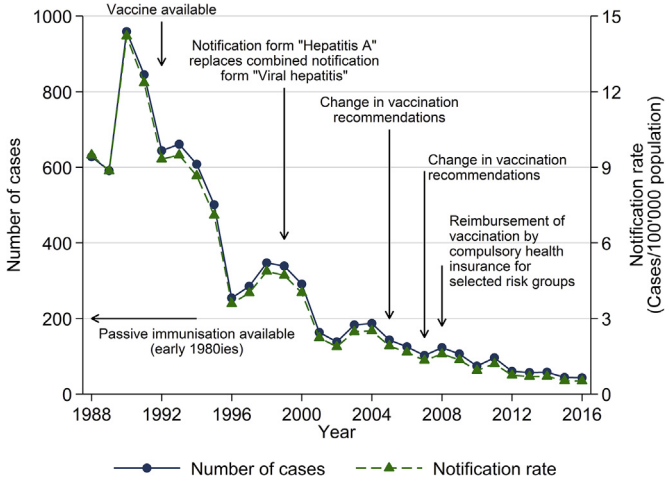

Fig. 1. Trend in number of reported hepatitis A cases and notification rate from 1988–2016 with major "events" (e.g. concerning vaccination) labelled, Switzerland.

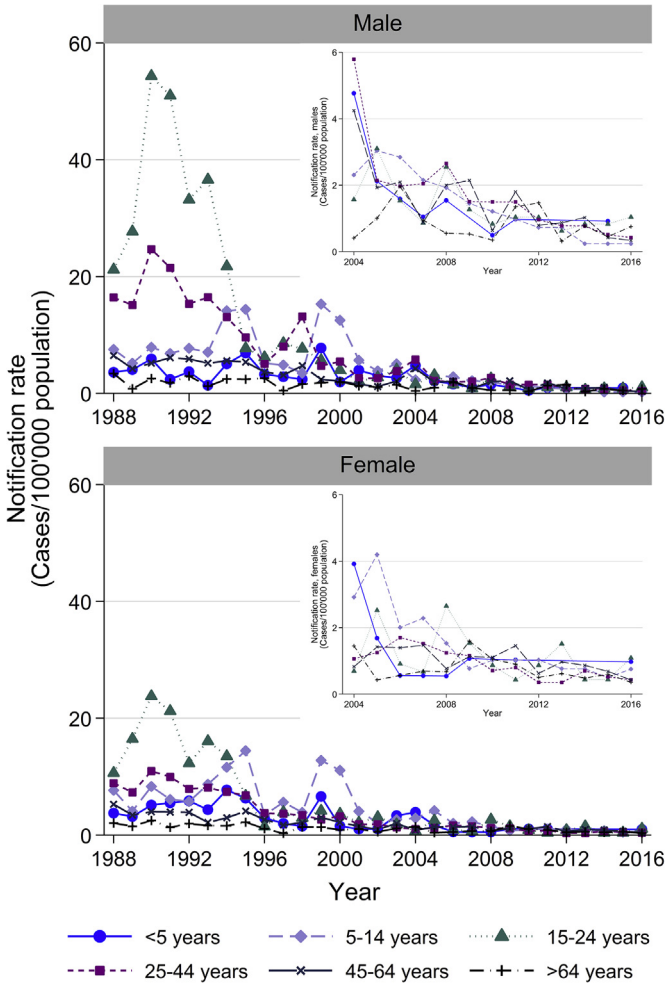

Fig. 2. Male and female hepatitis A notification rate by age group and year, 1988–2016, Switzerland.

onset and 7 received vaccination between 14 and 28 days before disease onset. For one case, the date of last vaccination was after disease onset. However, it was reported that this case received 3 doses of HA vaccine, the first one in the year prior to disease onset in mid-January. For the remaining 21 cases, disease onset was reported between 31 days and 14 years after their last (or only) vaccination.

3.2. Clinical characteristics

Jaundice was reported for 65.0–76.7% and increased transaminases for 57.1–86.6% of cases over all notification periods (Table 3). Other reported signs and symptoms included fever, gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhoea), reduced general state, weakness, myalgia, arthralgia, dark urine and pale stools. Fever, listed on the notification form since 2015, was specified for 39.3% of cases since 2015 but only for 2.9% of cases between 1999 and 2014 (no option to list "other symptoms" before 1999).

The proportion of hospitalised cases increased from 21.4% in 1988–1993 to 44.7% in 2012–2016 (Table 3, Fig. 3a). The number of cases with hospitalisation indicated as "yes" on the report on clinical findings is much lower than the number of hospitalisations due to ICD-10 codes B15.0 and B15.9 according to Swiss hospital statistics from 1998 to 2015 (the years for which hospital statistics were available; Fig. 3b). However, when considering only main diagnoses (as opposed to main and secondary diagnoses), numbers from the two statistics are comparable. The reason for hospitalisation (due to HA and/or for other reason) has been included in the reporting form since 2006. In three quarters of cases (171/228) with this information available, HA was indicated as the reason for hospitalisation (including one case hospitalised due to HA and another reason).

Complications, recorded since 2006, were reported for 3.9% (32/818) of cases and included coagulopathy, acute or imminent liver failure, cholecystitis, and general malaise.

Official mortality statistics, coded according to ICD-10, were available for 1995–2014. During this time period, 46 HA-related deaths were recorded (ICD-10 codes B15.0 and B15.9 as main or secondary cause). In the notification data, only 14 deaths among HA cases were captured during this time period (36 deaths from 1988–2016).

3.3. Reported location of exposure and exposure risks

Exposure abroad (or both, in Switzerland and abroad) increased from 39.3% in 1988–1993 to 58.1% in 2012–2016 while the proportion of "unknown or not specified" location of exposure decreased (Table 3).

European followed by African countries were most frequently mentioned as countries of exposure in the past. In the most recent years, exposure in African countries was more frequently reported (Table 3). The proportion of cases exposed in the Americas, Asia and Australia remained stable over the entire time period. Italy, Turkey and Germany were the three most frequently mentioned European countries between 2012 and 2016 while from 1988–1993 Italy, Spain and former Yugoslavia were lead exposure countries. Morocco, Tunisia, Egypt and Kenya were most frequently mentioned African countries from 1988–1993 and Morocco, Egypt, Togo, Ethiopia and Cap Verde from 2012–2016.

For the majority of cases (50.5%–58.9% for all notification periods), the source of exposure was reported to be unknown or was not specified. Intravenous drug use was the most frequently reported exposure risk in the 1988–1993 notification period while this exposure risk was not mentioned in the 2012–2016 period (Table 3). In contrast, the proportion of cases for which contaminated food or beverages was indicated as exposure risk increased over the years (2.2% of cases in 1988–1993; 28.5% of cases in 2012–2016). The mentioning of "contact with an infected person" as exposure risk decreased over the observation period (18.2% in 1988–1993; 12.6% in 2012–2016) while "sexual contact with an infected person" remained stable at around 4%. Exposure risks mentioned in the "other" category included occupational exposures, exposure to blood or blood products (including transfusions), or (previous and/or current) residency abroad.

4. Discussion

Our analysis of Swiss hepatitis A notification data from 1988–2016 revealed temporal trends in case numbers and case characteristics which may be caused by changes in disease epidemiology but also are likely to reflect changes in disease reporting and notification.

4.1. No unexpected risk group for HAV infection according to Swiss notification data

Recently published analyses of HA notification data in Switzerland included data until 2004 apart from a recent article of the FOPH reporting on an increase in case numbers in early 2017 [14,20,21]. All analyses except of the latter documented decreasing trends regarding HA notification rates that continue into contemporary times. Today, the notification rate in Switzerland is comparable for all age groups and for males and females, though fluctuating quite substantially in the setting of low case numbers. In contrast, the notification rate of 2014 in 30 EU/EEA countries was still highest for the 5–14 year age group, followed by the 0–4 and the 15–24 year age groups, and slightly higher in males compared to females [13].

The strongest decline in HAV notifications started in 1990, even before the introduction of HAV vaccination in Switzerland (Fig. 1).

Table 3
Characteristics of notified hepatitis A cases, 1988–2016, Switzerland.

	1988–1993, % (N)	1994–1999, % (N)	2000–2005, % (N)	2006–2011, % (N)	2012–2016, % (N)	All cases, 1988–2016, % (N)
Total cases	**(4328)**	**(2334)**	**(1105)**	**(626)**	**(262)**	**(8655)**
Possible case	– (0)	– (0)	– (0)	7.0 (44)	8.4 (22)	0.8 (66)
Probable case	0.3 (14)	1.1 (25)	0.2 (2)	4.5 (28)	4.2 (11)	0.9 (80)
Confirmed case	0.6 (27)	11.0 (256)	89.8 (992)	78.4 (491)	87.4 (229)	23.1 (1995)
Case not classified	99.1 (4287)	88.0 (2053)	10.0 (111)	10.1 (63)	– (0)	75.3 (6514)
Sex						
Male	64.2 (2779)	60.5 (1412)	60.1 (664)	56.1 (351)	51.7 (136)	61.7 (5342)
Female	34.5 (1494)	38.9 (908)	39.4 (435)	43.6 (273)	48.3 (126)	37.4 (3237)
Not specified	1.3 (55)	0.6 (14)	0.5 (6)	0.3 (2)	– (0)	0.9 (77)
Age group, years						
< 5	2.4 (103)	5.1 (120)	5.6 (62)	3.2 (20)	1.5 (4)	3.6 (309)
5–14	7.6 (330)	19.8 (462)	23.1 (255)	12.8 (80)	9.2 (24)	13.3 (1151)
15–24	35.1 (1517)	16.4 (382)	12.3 (136)	11.2 (70)	15.6 (41)	24.8 (2146)
25–44	40.4 (1750)	39.1 (912)	33.6 (371)	32.9 (206)	25.6 (67)	38.2 (3306)
45–64	10.2 (441)	15.2 (355)	18.8 (208)	28.4 (178)	30.9 (81)	14.6 (1263)
> 64	2.7 (116)	4.2 (99)	6.6 (73)	11.5 (72)	17.2 (45)	4.7 (405)
Not specified	1.6 (71)	0.2 (4)	– (0)	– (0)	– (0)	0.9 (75)
Total cases with notification on clinical findings	**80.9 (3503)**	**89.5 (2088)**	**93.0 (1028)**	**91.4 (572)**	**93.9 (246)**	**85.9 (7437)**
Nationality						
Swiss/Liechtensteiner	70.2 (2458)	62.2 (1299)	63.4 (652)	62.6 (358)	60.2 (148)	66.1 (4915)
Foreign	13.5 (472)	21.1 (441)	22.4 (230)	21.2 (121)	25.6 (63)	17.8 (1327)
Not specified	16.4 (573)	16.7 (348)	14.2 (146)	16.3 (93)	14.2 (35)	16.1 (1195)
Reported location of exposure						
Switzerland	< 0.1 (1)	3.2 (66)	33.4 (343)	27.3 (156)	25.6 (63)	8.5 (629)
Switzerland and abroad	– (0)	< 0.1 (1)	1.7 (17)	4.7 (27)	2.4 (6)	0.7 (51)
Abroad[a]	39.3 (1375)	46.5 (971)	42.2 (434)	51.9 (297)	55.7 (137)	43.2 (3214)
Europe[b]	38.3 (527)	49.0 (476)	38.6 (174)	34.9 (113)	25.2 (36)	40.6 (1326)
Africa[b]	24.0 (330)	17.6 (171)	22.0 (99)	34.0 (110)	37.1 (53)	23.4 (763)
America[b]	18.0 (247)	17.4 (169)	18.8 (85)	11.1 (36)	17.5 (25)	17.2 (562)
Asia[b]	17.3 (238)	12.7 (123)	14.4 (65)	16.0 (52)	19.6 (28)	15.5 (506)
Australia[b]	0.4 (6)	1.2 (12)	0.7 (3)	0.3 (1)	1.4 (2)	0.7 (24)
Not specified[b]	3.6 (49)	3.3 (32)	6.4 (29)	4.9 (16)	0.7 (1)	3.9 (127)
Unknown or not specified	60.7 (2127)	50.3 (1050)	22.8 (234)	16.1 (92)	16.3 (40)	47.6 (3543)
Reported exposure risk[a]						
Food/beverages	2.2 (76)	8.7 (181)	22.0 (226)	25.3 (145)	28.5 (70)	9.4 (698)
Contact with infected person	18.2 (639)	21.6 (451)	17.6 (181)	11.2 (64)	12.6 (31)	18.4 (1366)
Sexual contact with infected person	3.5 (124)	5.5 (115)	2.9 (30)	4.0 (23)	4.1 (10)	4.1 (302)
Intravenous drug user	33.4 (1171)	10.0 (208)	1.7 (17)	0.3 (2)	– (0)	18.8 (1398)
Other	3.3 (117)	5.0 (105)	2.8 (29)	3.7 (21)	3.7 (9)	3.8 (281)
Unknown or not specified	50.5 (1768)	57.3 (1197)	56.0 (576)	58.9 (337)	58.9 (145)	54.1 (4023)
Immunisation status						
Vaccinated[c]	4.5 (158)	3.1 (64)	2.4 (25)	4.5 (26)	4.9 (12)	3.8 (285)
Vaccinated with 1 dose[d]	0.6 (1)	6.3 (4)	48.0 (12)	57.7 (15)	66.7 (8)	14.0 (40)
Vaccinated with ≥2 doses[d]	– (0)	– (0)	16.0 (4)	30.8 (8)	8.3 (1)	4.6 (13)
Not specified[d]	99.4 (157)	93.8 (60)	36.0 (9)	11.5 (3)	25.0 (3)	81.4 (232)
Not vaccinated or not specified	95.5 (3345)	96.9 (2024)	97.6 (1003)	95.5 (546)	95.1 (234)	96.2 (7152)
Manifestation[a]						
Jaundice	74.1 (2596)	75.9 (1585)	76.7 (788)	70.1 (401)	65.0 (160)	74.4 (5530)
Transaminase increased ≥2.5 fold	70.1 (2457)	57.1 (1192)	76.8 (790)	83.4 (477)	86.6 (213)	69.0 (5129)
Other	– (0)	0.4 (10)	4.7 (52)	19.2 (120)	39.3 (103)	3.8 (285)
None	1.2 (41)	1.6 (33)	3.0 (31)	1.6 (9)	1.2 (3)	1.6 (117)
Unknown or not specified	12.9 (451)	9.5 (199)	5.3 (54)	2.8 (16)	2.8 (7)	9.8 (727)
Hospitalisation						
Yes	21.4 (750)	20.0 (418)	24.8 (255)	30.6 (175)	44.7 (110)	23.0 (1708)
Due to hepatitis A[e]	– (0)	– (0)	0.4 (1)	56.6 (99)	63.6 (70)	10.0 (170)
Other reason	– (0)	– (0)	– (0)	21.1 (37)	18.2 (20)	3.3 (57)
Due to hepatitis A and other reason[e]	– (0)	– (0)	– (0)	– (0)	0.9 (1)	0.1 (1)
Unknown or not specified[e]	100 (750)	100 (418)	99.6 (254)	22.3 (39)	17.3 (19)	86.7 (1480)
No or not specified	78.6 (2753)	80.0 (1670)	75.2 (773)	69.4 (397)	55.3 (136)	77.0 (5729)
Complications						
Yes	– (0)	– (0)	– (0)	3.7 (21)	4.5 (11)	0.4 (32)
No or not specified	100 (3503)	100 (2088)	100 (1028)	96.3 (551)	95.5 (235)	99.6 (7405)
Death						
Yes	0.5 (19)	0.4 (8)	0.1 (1)	0.9 (5)	1.2 (3)	0.5 (36)
Due to hepatitis A[f]	15.8 (3)	12.5 (1)	– (0)	– (0)	– (0)	11.1 (4)
Other reason[f]	10.5 (2)	50.0 (4)	100 (1)	100 (5)	100 (3)	41.7 (15)

(*continued on next page*)

Table 3 (*continued*)

	1988–1993, % (N)	1994–1999, % (N)	2000–2005, % (N)	2006–2011, % (N)	2012–2016, % (N)	All cases, 1988–2016, % (N)
Unknown or not specified[f]	73.7 (14)	37.5 (3)	– (0)	– (0)	– (0)	47.2 (17)
No or not specified	99.5 (3484)	99.6 (2080)	99.9 (1027)	99.1 (567)	98.8 (243)	99.5 (7401)

[a] Multiple answers possible.
[b] % among cases with exposure "Switzerland and abroad" or "abroad".
[c] Occasionally reported for cases already before 1992 when hepatitis A virus (HAV) vaccination was introduced. It cannot be determined whether these cases received passive immunisation against HAV (which was available already before 1992) or whether the information on the notification form was incorrect. It is suspected that physicians may not be able to easily differentiate active from passive immunisation based on information from vaccination cards and – in the absence of vaccination cards – patients may confuse HAV and hepatitis B virus vaccination.
[d] % among all vaccinated cases.
[e] % among hospitalised cases.
[f] % among deceased cases.

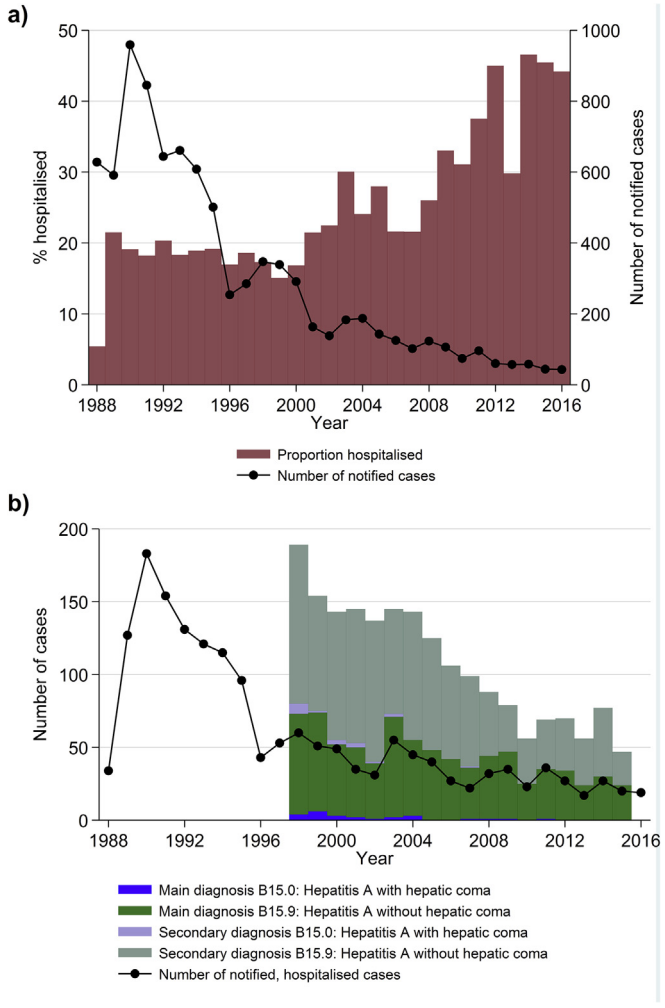

Fig. 3. (a) Proportion of hospitalised hepatitis A cases according to notification data (bars, left axis) and number of notified cases (line, right axis), and (b) hospitalisations due to hepatitis A according to notification forms (solid black line) and hospital statistics (bars; data for 1998–2015 only), 1988–2016, Switzerland.
Source of hospital statistics: Federal Statistical Office, Neuchâtel, Switzerland.

However, passive immunisation was already available since the early 1980ies [22]. Additionally, campaigns among IDUs could have contributed to the observed decline: The most frequently mentioned risk exposure in the early 1990s, intravenous/injecting drug use, has infrequently been reported in the last 10 years. It has been hypothesised that transmission of HA among IDUs could occur through sharing equipment or due to contaminated drugs or generally poor hygienic conditions [23,24]. Decreasing case numbers were also observed for hepatitis B together with a strong decline in IDU as reported risk exposure [25]. The decreasing case numbers were attributed to preventive measures introduced to control human immunodeficiency virus (HIV). The HIV/AIDS epidemic in the late 1980s and peak levels of drug consumption in the early 1990s resulted in the establishment of needle exchange facilities providing a "safe" environment for drug consumption [26]. A study among persons entering heroin-assisted treatment found that the proportion of HAV-infected persons decreased from 2003 to 2013 while the proportion of people vaccinated against HAV increased [27]. Nevertheless, the prevalence of HA is still higher in persons entering heroin-assisted treatment in Switzerland than among the general population [27]. Reports on IDU as a risk exposure among notified cases of HA from other countries are scarce. In Eastern Sydney, Australia, one third of notified cases was associated with IDU between September 1994 and June 1995 while this proportion dropped to 9% between July 1995 and December 1996 [28]. In New South Wales, Australia, recreational drug use decreased among reported HA cases between 2000 and 2009 [29]. In contrast, in Italy, the frequency of IDUs among cases of viral hepatitis (slightly more than half of which were HA cases) remained at constant but low levels (< 5%) between 1991 and 2006 [30]. Similarly, IDU was a reported risk factor for 2% of HA cases in 1994–1995 as well as in 2006–2007 in Arizona, United States [31].

HA vaccination failure and clinical cases of HA among vaccinated individuals reported in the literature are very rare [32–42]. Nevertheless, 3.8% of notified cases (285/7437) were reported to be vaccinated against HAV in Switzerland between 1988 and 2016. There are several explanations for this notably high proportion: (i) "vaccinated" cases might include persons having received passive immunisation (see also footnote in Table 2) which has only a short-term protective effect [1,43]; (ii) vaccination may have occurred only shortly before travel or in the framework of post-exposure prophylaxis – potentially too late to prevent disease onset (even though the notification form asked for vaccination status prior to infection); and (iii) HAV vaccination may be confused with other vaccinations, e.g. HBV vaccination, especially if information provided by physicians is obtained from patients rather than from vaccination cards (as it has been shown that travellers could frequently not recall their vaccination history [44]). Nevertheless, vaccination failure cannot be ruled out, especially in immunocompromised patients. A recent study among Swedish travellers under immunosuppressive medication due to reactive arthritis has shown that similar protection after two months can be achieved by administering a 3-dose regimen (1 + 1 + 1 or 2 + 1) at 0, (1) and 6 months compared to a 2-dose regimen at 0 and 6 months among healthy individuals [45].

The decline in the HA incidence led to an increase in the population susceptible to HAV in the EU/EEA which was not compensated by increased vaccination rates, as highlighted by Gossner *et al.* [3]. This is

assumed to be the case also in Switzerland in the absence of universal vaccination recommendation. However, data on population susceptibility are not available. Vaccination coverage was assessed in Switzerland for 2-, 8- and 16-year old children and adolescents and was 4% [95% confidence interval (CI): 3.2–4.6], 11% [95% CI: 9.5–11.7], and 28% [95% CI: 24.8–30.6] for two doses, and slightly higher for one dose, in 2014–16 [46]. Between 2002 and 2012, 53.1% of travellers seeking pre-travel health advice in one Swiss travel clinic received HAV vaccination (in part combined with HBV vaccination) [47]. On the other hand, a survey among travellers to tropical and subtropical countries at a Swiss airport in 2002 revealed that only 26% of travellers were protected against HAV and an additional 12% were potentially protected [48]. It has to be considered that surveys conducted at the airport might be biased (over-representing frequent travellers, and considering only one mode of transport) as highlighted by Pedersini *et al.* (2016) [44]. They showed that the frequency of international travel and endemicity at destination are both associated with HA vaccination among travellers in five European countries. In 2014, 62.6% of MSM reported to be vaccinated against HAV in a Swiss online survey among MSM [49]. Further insights into vaccination rates and knowledge about HA among Swiss MSM are expected once the data from the European MSM Internet Survey (EMIS-2017) becomes available [50].

Recently, HAV outbreaks among MSM have been reported in several European countries [51] including England [52], the Netherlands [53] and Germany [54]. Our analysis did not suggest any similar outbreak among MSM in Switzerland: in 2016 sexual contact with an infected person was specified as a risk exposure only for one case and the male-to-female ratio did not change compared to 2015. However, case notifications for HAV more than doubled in the first 22 weeks of 2017 compared to the same time period in 2016 (41 *vs.* 17 cases) [21]. A link to the European outbreaks among MSM seems likely considering that the increase in case numbers mainly affects males.

"Exposure abroad" was indicated for more than half of recently notified cases, suggesting that travelling is still a main risk factor for acquiring HA. Previous analyses of Swiss HAV notification data identified risk groups or different exposure patterns among subgroups of notified cases (e.g. among cases below 20 years of age, those with Swiss nationality tended to be exposed in Switzerland while those with foreign nationality tended to be exposed abroad [14]). We did not conduct such subgroup analyses considering the low case numbers in recent years.

4.2. Relative increase in hospitalisations

Data on hospitalisations revealed two interesting trends: (i) the proportion of hospitalised patients increased among reported cases, and (ii) hospital statistics suggest substantial underreporting of hospitalisations due to HA in the NNSID. An increasing proportion of hospitalisations has also been reported in the United States [55]. Ly and Klevens hypothesised that this observation is explained by a shift of the susceptible population towards older adults together with the fact that HA leads to more severe disease with increasing patient age. This is likely also the case for Switzerland: while the median age of reported cases was 26 and 25 years in non-hospitalised (incl. hospitalisation status not specified) and hospitalised patients, respectively, in 1988–1993, median age for those two groups increased to 36.5 and 47 years in 2012–2016. An alternative explanation links the decreasing frequency of HAV infection in Switzerland (or at least the decreasing notification rate) to physicians' decreasing awareness for the disease, especially in patients with mild manifestations.

The number of hospitalisations according to hospital statistics is comparable with the number of hospitalised cases according to notification data when considering the main diagnosis in hospital statistics. When also considering secondary diagnoses, hospital statistics suggest more than double the number of HA cases compared to notification data (Fig. 3b). It should be considered that re-admission of the same patient is counted as a new case in Swiss hospital statistics except if re-admission occurs within 18 days and in the same hospital (personal communication, FSO, 11 July 2017). Still, we believe that the striking difference between hospital statistics and notification data is not fully explained by re-admissions alone. We also speculate that the observed difference, apart from under-notification, could arrive from GPs completing notification forms before the patient is hospitalised. If the hospital physician then does not complete another notification form (assuming or knowing that the case was already reported by the GP), the patient's hospitalisation is not captured by the NNSID. The same probably applies to mortality data.

4.3. System changes influence trends in notification data

The notification form is provided by and submitted to the FOPH. The notification form was changed several times between 1988 and 2016, as were case definitions, classifications and data entry procedures. All these changes are difficult to document *post-hoc* for the purpose of this study and to separate from each other; they make interpretation of long-term trends difficult. In the following we discuss such issues using examples from Swiss HA notification given that these experiences likely also apply for other diseases and surveillance systems.

Introducing a new variable on the notification form is a change which is relatively easy to track as it leads to a rather abrupt change in the data. The location of exposure to HAV could be recorded as "abroad" before 1999 and as "abroad" and/or "in Switzerland" thereafter. In the notification data, this is reflected in a sudden increase in the proportion of cases exposed in Switzerland and a parallel drop in the "unknown or not specified" category.

Similarly, the "reason for hospitalisation" and "complications" were included on the form probably only since 2006 (notification forms for 2002–2005 were not available to check). Such changes can potentially be noticed even if old notification forms are not available, but their impact is difficult to quantify. In contrast, more subtle changes, e.g. in wording can also influence answers given, but might not be easily recognisable in the absence of actual notification forms or stringent documentation of changes on the reporting forms. For example, main features of HA (increased transaminases and jaundice), were recorded from 1988 until 2016. Nevertheless, changes occurred repeatedly: from 1988–1990, they were listed under the heading "clinic". From 1991–1998, they were listed under the heading "reason for laboratory test" while since 1999 they are part of the section on "manifestation". Also, in 1999 the wording changed from "increased transaminases" to "transaminase(s) $\geq 2.5\times$ ↑". While asking for symptoms under the headings "clinic" and "manifestation" are likely to result in the same responses, the heading "reason for laboratory test" might not: a symptom might be present but not be considered the reason for laboratory testing and hence, not checked on the form.

Another, potentially important, change: up until 1998, all cases of viral hepatitis were captured using the same notification form entitled "Viral hepatitis". Only since 1999, separate notification forms exist for hepatitis A, B, and C (other types of viral hepatitis are not reportable as per 2017). At the same time, the notification form was revised substantially. Revisions of notification forms are complex processes involving a number of people and perspectives; we exemplify the Swiss experience: the expert analysing the notification data for a given disease tries to get the most relevant information needed for appropriate interpretation of the epidemiology. Managers of the overall notification system (including data entry and management), and hence, with a view on all notifiable diseases, try to avoid long notification forms, frequent changes and heterogeneous forms – e.g. once asking for nationality, once for country of origin, and once for country of birth. Furthermore, information should not be too difficult to obtain/know by laboratory personnel or physicians (those requested to complete the forms), otherwise compliance will be low. Finally, the legal department will

critically review the forms aiming at reducing the personal information obtained to the essentials for fulfilling the mandate of the FOPH for early detection, monitoring, prevention and containment of communicable diseases.

In summary, changes in notification forms and procedures may be needed at times, but should be kept to a minimum in order to allow analysis and interpretation of long-term trends. This in turn is only possible if changes made are meticulously documented.

4.4. System-inherent limitations

Patients' information is provided by physicians in charge of HA patients. However, it is not known how complete and systematically they assess e.g. exposure history. Assessing exposure risks in a systematic fashion is likely not a priority of physicians given that the source of infection does not matter for treatment. This is reflected in the high proportion of cases (> 50%) for which exposure risk is indicated as "unknown" or not specified at all. We hypothesise that "traditional" (well-known) risk factors are often overestimated compared to less known risk exposures in surveillance systems. This could also be a reason for the observed increase in "contaminated food and/or water" mentioned as risk exposure: in the absence of "specific" risk factors such as IDU and travel, physicians may be choice-biased being tempted to indicate "contaminated food and/or water" instead of ticking "unknown" or not indicating any risk factor(s).

Probably almost every person has consumed a food item which could have been contaminated with HAV during the relevant time window of 15–50 days before symptom onset. At the same time, reports of foodborne outbreaks of HA – recently frequently associated with fresh and frozen berries and fruits [56–61] – could also have increased awareness that HAV can be transmitted through contaminated food. The rather long incubation period, together with a wide range, and more or less non-specific or ubiquitous risk exposures could also explain the high proportion of unknown or unspecified exposure risks. Suspected sources of infection are usually not followed-up, unless there is evidence of an outbreak. Therefore, location of exposure remains speculative as long as no mandated research studies are conducted.

Furthermore, the surveillance system is likely to capture mainly severe and/or "typical" cases as these are most likely to undergo laboratory testing. Gastroenteritis patients reporting recent travel were found to have a 3.6 times increased odds for stool testing compared to patients not reporting travel in the 7 days preceding symptom onset [62]. Similarly, we suspect that travel-related HA cases (or patients with a history of recent travel) are more likely to be captured by the NNSID. This may not compromise validity of the surveillance system, but should be born in mind when interpreting surveillance data.

In contrast, we have anecdotal evidence from notification forms that physicians suspect transmission from a (symptomatic or asymptomatic) contact person who had been travelling recently, but the patient him-/herself (the suspected secondary case) stayed in Switzerland. These HA cases would no longer be considered an imported/travel-related case as the reported patient did not travel and was indeed exposed in Switzerland. Hence, the distinction between imported and autochthonous cases might be flawed.

Similarly, the importance of migrants and travellers visiting friends and relatives (VFR) is difficult to evaluate: on the one hand, those born in high-endemicity countries could already be immune and hence, increase population seroprevalence in Switzerland. On the other hand, young children having visited their home country (or the home country of their parents) could be asymptomatically infected and spread the disease once back in Switzerland. Generally it is known that VFR are at increased risk of infectious diseases during travel [63–65], they are less likely to seek pre-travel health advice [65–67] and are less adherent to pre-travel health advice [68,69].

Furthermore, it is not known how often contact persons of HA cases are tested and how this may influence notification data. Testing may be considered unnecessary for both, secondary cases showing clear and typical signs and symptoms, and (potential) secondary cases not showing any signs and symptoms of HAV infection.

4.5. Conclusions

Hepatitis A incidence is declining globally including in Switzerland, apart from outbreaks (such as the recent European outbreak among MSM). Case numbers have been low in recent years. However, considering that the population is becoming increasingly susceptible to HAV infection and hence, the probability of outbreaks is increasing, it is important to strengthen surveillance and prevention efforts as shown by the recent outbreak among MSM in Europe.

Current Swiss notification data on HAV do not allow reliably identifying existing (IDU, MSM, travellers) and potential new risk groups as information on exposure to HAV available to and provided by physicians is limited and case numbers are low. Patient information on exposure is often poorly filled in on the notification forms. Thus, changes in NNSID data or outbreaks need to be followed up with in-depth investigations to understand contemporary transmission patterns.

Thorough understanding of physicians' approaches to diagnose a patient with HAV infection, changes in notification forms, case definition, case classification, and data entry is required for correct interpretation of notification data. Additionally, research studies are needed to complement information from routine surveillance to answer specific questions such as estimating levels of under-ascertainment, under-diagnosis and under-notification, or evaluating best practices to collect data on exposure. Such complementary information is especially important for interpretation of long-term trends of hepatitis A in particular and of highly dynamic diseases and surveillance systems in general.

Authors' contributions

DM, CS and MJ conceptualised the study. MJ extracted the data. CS developed and carried out the statistical analysis. CS, DM and MJ interpreted the results. CS wrote the first draft of the manuscript. DM and MJ contributed to the writing and revision of the manuscript. All authors approved the final version.

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Conflicts of interest

MJ is working at the Federal Office of Public Health and contributed to this project/article in her capacity as public health specialist and her function as scientific collaborator within the organisation.

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