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Severity of the clinical presentation of hepatitis A in five European countries from 1995 to 2014

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ABSTRACT

Objectives: We analysed hepatitis A (HepA) notifications and hospitalisations in Italy, the Netherlands, Norway, Spain, and Sweden for available periods between 1995 and 2014. We aimed to investigate whether decreasing HepA incidence is associated with increasing age at infection and worsening HepA presentation and to identify groups at risk of severe disease.

Methods: We performed a retrospective cohort study including 36 734 notified and 36 849 hospitalised patients. We used negative binomial regressions to identify over time: i) trends in hospitalisation and notification rates; ii) proportion of hospitalised and notified patients aged ≥40 years; iii) proportion of "severe hospitalisations"; and iv) risk factors for severe hospitalisation.

Results: During the study period both HepA notifications and hospitalisations decreased, with notification rates decreasing faster, patients aged ≥40 years increased, however, the proportion of severe HepA hospitalisations remained stable. Older patients and patients with comorbidities, particularly liver diseases, were more likely to experience severe disease.

Conclusions: We used digitalised health information to confirm decreasing trends in HepA hospitalisations and notifications, and the increasing age of patients with HepA in Europe. We did not identify an increase in the severity of the clinical presentation of patients with HepA. Older patients with liver diseases are at increased risk of severe disease and should be prioritised for vaccination.

Introduction

Hepatitis A virus (HAV) infection confers lifelong immunity and does not result in chronic infection (Koff, 1998). The proportion of symptomatic infections and the severity of the disease increase with age. Overall, the case fatality is generally low (0.1 to 0.3%) but increases (1.8%) in older adults or persons with underlying chronic liver disease (American Public Health Association, 2016; Koff, 1998;

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Pramoolsinsap et al., 1999; Steffen et al., 1994; Vento et al., 1998). This epidemiological profile is also reflected in the fact that in high endemicity countries, where HAV transmission occurs at high rates, most infections occur asymptomatically in young children. However, in low endemicity countries, infections more often occur in susceptible adults that manifest as severe acute hepatitis and may need hospitalisation owing to fulminant hepatitis or acute liver failure that may result in death (Kim et al., 2010; Lemon et al., 2017; Prevention of hepatitis A through active or passive immunization: Recommendations of the Advisory Committee on Immunization Practices, 1999; Shin et al., 2014). Thus, it has been hypothesised that long-term decreasing HAV transmission is associated with an increased proportion of severely ill patients, as documented in South Korea (Kim and Lee, 2010; Lemon et al., 2017). However, it is unknown whether the same has been witnessed in the European Union/European Economic Area (EU/EEA) in the last 2 decades.

Most countries of the EU/EEA currently experience very low or low HAV endemicity (Carrillo-Santisteve et al., 2017). The transition from higher endemicity to the current levels occurred at different times throughout Europe. The current endemicity in Europe is related to past HAV infection incidence and follows a gradient from low to higher endemicity from northern to southern, and then to eastern Europe (Carrillo-Santisteve et al., 2017). Although European Nordic countries observed low hepatitis A (HepA) incidence already in the 1950s, southern EU countries observed a decline in incidence between the 1970s and the 1990s. The same trajectory took place in recent decades in the eastern EU and is partially taking place at present (Carrillo-Santisteve et al., 2017).

In very low/low endemicity settings, HAV transmission is partially driven by sporadic but cyclical outbreaks. Because most children escaped HAV infection in recent decades, outbreaks often affect susceptible adults and are associated with consumption of contaminated food items or affects selected groups at increased risk of infection. The latter include for example susceptible travellers to endemic countries, ethnic minorities, men who have sex with men (MSM), and people who inject drugs (Gallian et al., 2019; Hrivniakova et al., 2009; Latimer et al., 2007; Ndumbi et al., 2018; Ruscher et al., 2020; Sane et al., 2015; Severi et al., 2015; Zimmermann et al., 2021).

A safe and effective HepA vaccine has been commercialised since the mid-1990s. As per World Health Organization (WHO) recommendations, in most EU/EEA countries the vaccine is recommended only for susceptible individuals at increased risk of infection (World Health Organization, 2019, 2012). Only Greece, Apulia in Italy, and Catalonia, Ceuta, and Melilla in Spain offer vaccination to toddlers and adolescents (European Centre for Disease Prevention and Control, 2016).

In most EU/EEA countries, HepA is a notifiable disease and comprehensive case-based national surveillance is conducted (European Centre for Disease Prevention and Control, 2022; European Commission, 2012). HepA notifications gather information on the characteristics of reported cases and related risk factors, and little data are collected on the severity of the clinical presentation. Better information on the severity of the clinical presentation of hospitalised HAV cases can be extracted from national hospitalisation databases, which are available electronically in some EU/EEA countries.

Our study aimed at assessing whether the severity of HepA presentation increased in the last 3 decades in selected EU/EEA countries. To achieve this, we tested the following hypotheses: i) HepA notification rates decreased during the study period; ii) HepA hospitalisations also decreased during the same time, but at a lower rate than notifications; iii) patients' age at HAV infection increased both in notified and hospitalised cases during the study period; iv) the proportion of hospitalisations with a severe outcome increased during the same time; v) finally, cases experiencing a severe outcome have specific characteristics.

Methods

Study design and population

We designed a retrospective cohort study. The study population consisted of all notified patients with HepA as well as hospitalised patients with HepA in Italy, the Netherlands, Norway, Spain, and Sweden for the available periods between 1995 and 2014.

Italy contributed notification and hospitalisation data for the years 2001-2013; the Netherlands for 1999-2010; Norway for 2000-2014; Spain for 1997-2013 (with hospitalisations from the whole country but notifications not including those from Catalonia because these data were only available only for a part of the study period); and Sweden for 1995-2012, with both notification and hospitalisation data available for 1997-2010 (Table 1).

Data collection

We extracted HepA notifications from national HepA surveillance databases. We retrieved hospitalisation data through the collection of hospital discharge forms and extracted these based on International Classification Of Diseases, 9th Revision codes ("070.1", HepA without hepatic coma, and "070.0", HepA with hepatic coma) and International Classification Of Diseases, 10th Revision ("B15.9", HepA without hepatic coma, and "B15.0", HepA with hepatic coma). We excluded patients hospitalised for a single day without overnight hospitalisation. Data on notifications and hospitalisations were from 2 different sources in each country and it was not possible to link them.

Analysis

We described notified and hospitalised cases by reporting year, age (categorised in 4 age-groups: $<$18 years; 18-39 years; 40-64 years; and $\geq$65 years) and sex. For hospitalised cases, we also described length (median and interquartile range [IQR]) and number of hospitalisations (categorised as $\geq$3 or $<$3 hospitalisations), and the distribution of critical outcomes (hepatic coma, liver transplant, and in-hospital death), and comorbidities (categorised as "no comorbidities", "liver disease", and "other comorbidities"). Information on liver transplants was not available for Dutch and Norwegian patients; comorbidities were not available for Norwegian hospitalised patients. We categorised hospitalisations as "primary" (HepA reported as the main cause of hospitalisation), and "secondary" (hospitalisation main cause different from HepA, but HepA listed as 1 of the conditions occurring during hospitalisation). We defined "severe hospitalisations" based on at least 1 of the following conditions during hospitalisation: death, liver transplant, hepatic coma, $\geq$3 courses of hospitalisations with HepA, or hospitalisation length longer than 7 days. We collapsed multiple hospitalisations for the same patient (i.e. relapsing HepA) in a single hospitalisation with the date of admission corresponding to the date of first admission and the length of hospitalisation equal to the sum of the hospitalisation lengths of all collapsed hospitalisations. However, in Spain, this was possible only for those patients who were re-hospitalised within 30 days after a previous discharge in the same hospital. Whereas, in Norway, this was possible only for the hospitalisations occurring in or after 2008.

We expressed HepA notification and hospitalisations rates during the study period as cases per 100 000 persons using mid-year population data. We plotted hospitalisation and notification rates along with related trend lines using linear regressions. We used negative binomial regression models to estimate trends by year

Table 1
Characteristics of the study population by reporting country, hepatitis A primary or secondary hospitalisation and notification in Italy, The Netherlands, Norway, Spain, and Sweden, 1995-2014

		Italy 2001-2013 [1]			The Netherlands 1999-2010 [1]			Norway 2000-2014 [1]			Spain 1997-2013 [1]			Sweden 1995-2012 [1]		
		Hep A primary hospitalis.	Hep A secondary hospitalis.	Hep A notific.	Hep A primary hospitalis.	Hep A secondary hospitalis.	Hep A notific.	Hep A primary hospitalis.	Hep A secondary hospitalis.	Hep A notific.	Hep A primary hospitalis.	Hep A secondary hospitalis.	Hep A notific. [2]	Hep A primary hospitalis.	Hep A secondary hospitalis.	Hep A notific.
Hospitalisations (n)		19 414	7394	16 958	341	117	2225	352	233	1027	5757	2273	14 199	639	329	2325 [3]
Females (n (%))		6461 (33)	3065 (41)	5645 (33)	132 (39)	42 (36)	869 (39)	151 (43)	79 (34)	410 (40)	1987 (34)	1091 (48)	5094 (36)	275 (43)	121 (37)	987 (42)
Age	<18 (n (%))	4343 (22)	392 (5)	4551 (27)	73 (21)	3 (3)	897 (40)	75 (21)	9 (4)	317 (31)	1694 (29)	177 (8)	4628 (33)	129 (20)	10 (3)	789 (34)
	18-39 (n (%))	10 383 (54)	1392 (19)	9019 (54)	116 (34)	23 (20)	714 (32)	109 (31)	75 (32)	336 (33)	3172 (55)	906 (40)	7535 (53)	265 (42)	80 (24)	885 (38)
	40-64 (n (%))	3937 (20)	2827 (38)	2915 (17)	112 (33)	65 (56)	519 (23)	128 (36)	106 (46)	292 (28)	751 (13)	781 (34)	1773 (12)	192 (30)	158 (48)	538 (23)
	65+ (n (%))	746 (4)	2827 (37)	340 (2)	40 (12)	26 (22)	95 (4)	40 (11)	43 (18)	82 (8)	140 (2)	409 (18)	263 (2)	53 (8)	81 (25)	113 (5)
Hospitalisation length	days (median - (IQR))	8 (6-13)	8 (4-16)	NA	4 (3-7)	7 (4-16)	NA	3 (2-6)	5 (2-11)	NA	5 (3-7)	6 (3-11)	NA	3 (2-5)	5 (2-11)	NA
Severe episodes	(n (%))	11 273 (58)	3993 (57)	NA	84 (25)	54 (46)	NA	52 (15)	86 (37)	NA	1248 (22)	868 (38)	NA	76 (12)	130 (40)	NA
>7 days hospitalised (n (%))		11 157 (58)	3992 (54)	NA	82 (24)	54 (46)	NA	47 (13)	83 (36)	NA	NA	868 (38)	NA	68 (11)	128 (39)	NA
≥3 hospitalisations (n (%))		104 (1)	56 (1)	NA	0 (0)	1 (1)	NA	0 [4] (0)	3 [4] (1)	NA	NA	20 (0.9)	NA	9 (1)	19 (6)	NA
Hepatic coma (n (%))		276 (1)	567 (8)	NA	3 (1)	0 (0)	NA	5 [4] (2)	11 [4] (4)	NA	97 (2)	71 (3)	NA	11 (2)	21 (6)	NA
Liver transplant (n (%))		11 (0)	5 (0)	NA	Na	Na	NA	Na	Na	NA	8 (0)	4 (0)	NA	1 (0)	0 (0)	NA
In hospital-death (n (%))		71 (0)	288 (4)	NA	4 (1)	0 (0)	NA	0 (0)	9 (4)	NA	21 (0)	0 (0)	NA	1 (0)	3 (1)	NA
Comorbidities	no (n (%))	13 789 (71)	NA	NA	220 (64)	NA	NA	Na	na	NA	2543 (44)	NA	NA	379 (59)	NA	NA
	liver disease (n (%))	1516 (8)	1741 (24)	NA	37 (11)	54 (46)	NA	Na	na	NA	666 (12)	483 (21)	NA	43(7)	174(53)	NA
	any other (n (%))	4109 (21)	5653 (76)	NA	84 (25)	63 (54)	NA	Na	na	NA	2548 (44)	1790 (79)	NA	217 (34)	155 (47)	NA

[1] Study timeframe for each country
[2] Not including Catalonia
[3] Available for data ≥1997
[4] Available for data ≥2008Hospitalis. = hospitalisation; notific. = notification; na = not available; NA = not applicable

over the study period for i) hospitalisation and notification rates; ii) proportion of hospitalised and notified patients aged ≥40 years to identify changes in the age distribution; and iii) proportion of severe hospitalisations.

Finally, we fitted a negative binomial regression model to identify risk factors for severe hospitalisation (outcome) during the study period. Predictors included in the analysis for all countries were age group (reference group: aged 18-39 years), sex, year of hospitalisation (numerical variable), and comorbidities. We fitted predictors in the model with a forward-stepwise approach based on the strength of the association and retained in the final model only those variables significantly associated with the outcome or explaining at least 10% of the variance of the incidence risk ratio (IRR). We express all univariate and multivariable associations IRR with corresponding 95% confidence intervals (95% CI). A p-value of ≤0.05 was considered statistically significant. Statistical analysis was performed using STATA v14.0 software (StataCorp, TX, USA).

Results

Descriptive analysis

In Italy, the Netherlands, Norway, Spain, and Sweden there were 36 734 HepA notifications and 36 849 hospitalisations during the study period (Table 1). Italy was the country contributing to the highest number of notifications (44.9%) and hospitalisations (72.0%).

In all countries and all groups the proportion of females was always below 50%, ranging from 33% in notified and primary HepA hospitalised patients to 48% in secondary HepA hospitalised patients.

The number of notified cases and primary HepA hospitalisations was highest in the group aged 18-39 years in all countries but the Netherlands, where most notifications were in the group aged <18 years, and Norway, where most HepA primary hospitalisations were in the group aged 40-64 years. The highest number of secondary HepA hospitalisations was in the group aged 40-64 years in all countries but Spain, where it was in the group aged 18-39 years.

The ratio of primary to secondary hospitalisations ranged from 1.5:1 in Sweden to 2.9:1 in The Netherlands. The median primary HepA hospitalisation length ranged from 3 days in Norway and Sweden to 8 days in Italy. The median secondary HepA hospitalisation length ranged between 5 days in Norway and Sweden to 8 days in Italy. In all countries, the median length of secondary hospitalisations was higher than for primary hospitalisations, except in Italy, where these were roughly the same.

Compared with the other 4 countries, Italy had the highest proportion of severe hospitalisations among patients with primary HepA hospitalisation (58%, versus a range from 12% in Sweden to 25% in the Netherlands, respectively) and among patients with secondary hepatitis (57%, versus a range from 37% in Norway to 46% in the Netherlands, respectively). The proportion of patients with hospitalisation length >7 days widely ranged between countries (from <11% for primary hospitalisations in Sweden to 58% for primary hospitalisations in Italy) and it was similar to the proportion of severe hospitalisations in each country. The highest proportion of patients hospitalised for ≥3 times in the same year was in Sweden (1% in patients with primary HepA hospitalisation and 6% in those with secondary HepA hospitalisation). In the other countries, the proportion was around or below 1%, both for primary and secondary HepA hospitalisations. Both hepatic comas (highest proportion reported in Italian secondary HepA hospitalisation: 7.7%) and in-hospital deaths (highest proportion reported in Italian and Norwegian secondary HepA hospitalisation: 3.9%) were more frequent in patients with secondary HepA hospitalisation, whereas liver transplants were rarely reported in both classes of patients (29 liver transplants reported overall).

Except for Norway (missing information) and Spain (where the proportion of patients without comorbidities or with comorbidities other than liver diseases was similar), in all other countries, most patients (≥59%) with primary HepA hospitalisation had no comorbidities. In secondary HepA hospitalisations, patients with other comorbidities were more frequent than those with liver disease, except in Sweden, where it was the opposite.

Embedded Table 2
Incidence risk ratio (IRR), p-value (p) and 95% confidence intervals (95% CI) of notification and hospitalisation rates by year, in Italy, the Netherlands, Norway, Spain, and Sweden, 1997-2014

Country-output	IRR	P	95% C.I.	
Italy-notifications	0.92	0.001	0.87	0.96
Italy-hospitalisations	0.90	<0.001	0.87	0.94
Netherlands-notifications	0.91	<0.001	0.86	0.95
Netherlands-hospitalisations	0.96	0.06	0.92	1.00
Norway-notifications	0.92	0.001	0.88	0.97
Norway-hospitalisations	0.94	0.001	0.90	0.97
Spain-notifications	1.03	0.23	0.98	1.09
Spain-hospitalisations	1.00	0.72	0.98	1.03
Sweden-notifications	0.89	<0.001	0.84	0.93
Sweden-hospitalisations	0.91	<0.001	0.88	0.95

Embedded Table 3
Incidence risk ratio (IRR), p-value (p) and 95% confidence intervals (95% CI) of the proportion of notified and hospitalised cases older than 40 years, by year, in Italy, the Netherlands, Norway, Spain, and Sweden, 1995-2014

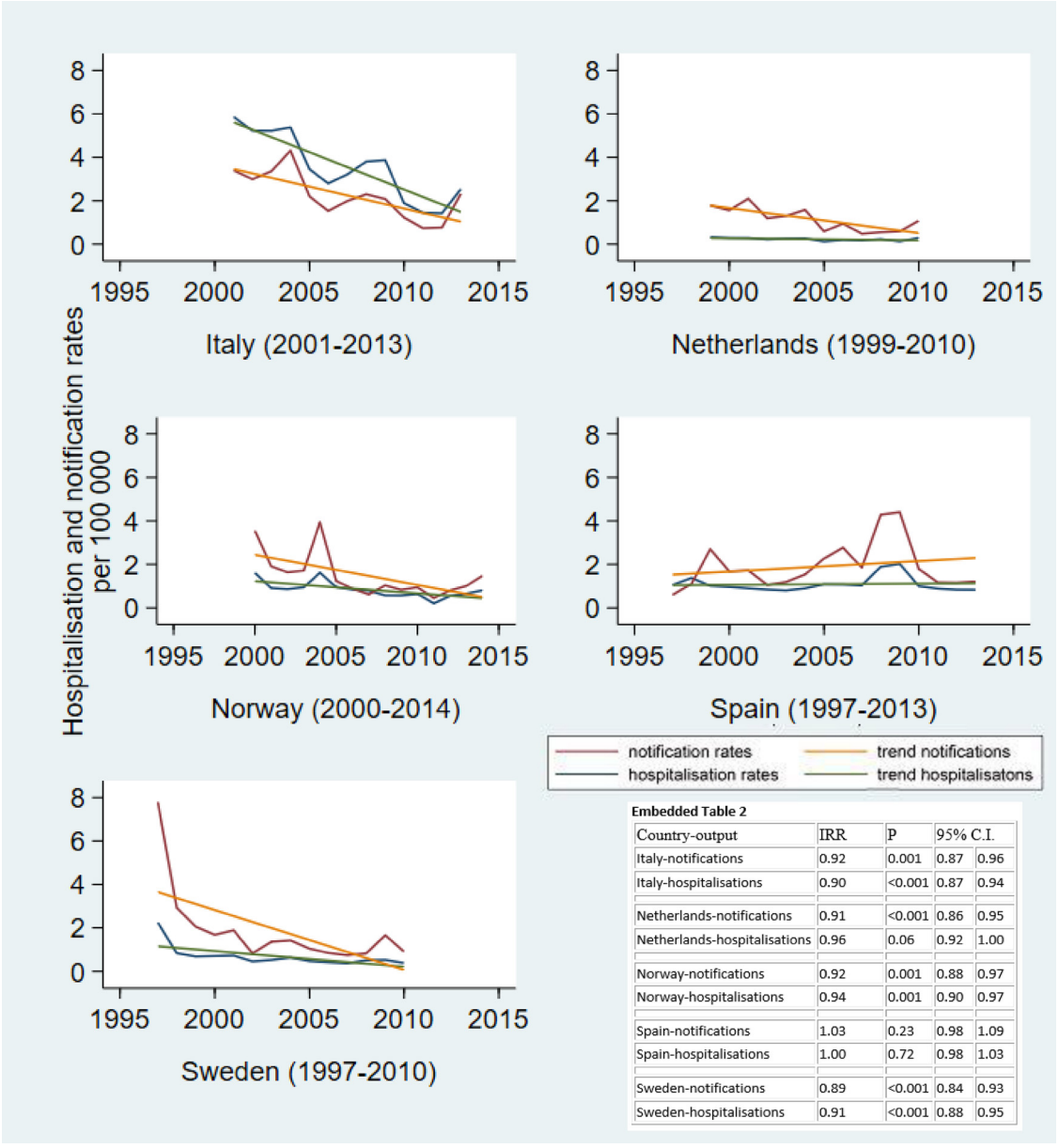
Country-output	IRR	P	95% C.I.	
Italy-notifications	1.08	<0.001	1.06	1.11
Italy-hospitalisations	1.02	<0.001	1.01	1.04
Netherlands-notifications	1.06	<0.001	1.04	1.08
Netherlands-hospitalisations	1.03	0.16	0.99	1.08
Norway-notifications	1.03	0.04	1.00	1.05
Norway-hospitalisations	1.01	0.60	0.98	1.03
Spain-notifications	1.11	<0.001	1.08	1.14
Spain-hospitalisations	1.07	<0.001	1.06	1.08
Sweden-notifications	0.99	0.52	0.97	1.02
Sweden-hospitalisations	1.04	<0.001	1.02	1.06

Trends in hospitalisations versus notifications

In Italy, the Netherlands, Norway, and Sweden, both notification and hospitalisation rates decreased over time with annual estimated decreases ranging from 11% (notifications in Sweden) to 4% (hospitalisations in the Netherlands). These decreases were all statistically significant except for the Dutch hospitalisations (P 0.06; Figure 1 and embedded Table 2). In the Netherlands, Norway, and Sweden, notification rates decreased more rapidly than hospitalisation rates; however, in all countries the estimates' 95% CI overlapped. In Spain, both rates were stable, with slightly positive, but not statistically significant estimates (P 0.23 for notifications and P 0.72. for hospitalisations).

Proportion of patients aged ≥40 years

In Italy, the Netherlands, Norway, and Spain, the proportion of notified patients aged ≥40 years increased over the study period, ranging from 3% to 11% per year. In Sweden, the trend in the proportion of notified patients aged ≥40 years was not statistically significant, with a decrease of 1% per year during the study period (Figure 2 and embedded Table 3). In all countries, the proportion of hospitalised patients aged ≥40 years increased over the study period; however, the estimates were statistically significant only in Italy and Spain, with increases ranging from 1% to 7%.



Embedded Table 2

Country-output	IRR	P	95% C.I.	
Italy-notifications	0.92	0.001	0.87	0.96
Italy-hospitalisations	0.90	<0.001	0.87	0.94
Netherlands-notifications	0.91	<0.001	0.86	0.95
Netherlands-hospitalisations	0.96	0.06	0.92	1.00
Norway-notifications	0.92	0.001	0.88	0.97
Norway-hospitalisations	0.94	0.001	0.90	0.97
Spain-notifications	1.03	0.23	0.98	1.09
Spain-hospitalisations	1.00	0.72	0.98	1.03
Sweden-notifications	0.89	<0.001	0.84	0.93
Sweden-hospitalisations	0.91	<0.001	0.88	0.95

Figure 1. Hepatitis A notification and hospitalisation rates per 100 000 population and corresponding trend lines over the study period, in Italy, the Netherlands, Norway, Spain, and Sweden, 1997-2014

Embedded Table 4
Incidence risk ratio (IRR), p-value (p) and 95% confidence intervals (95% CI) of the proportion of hospitalised patients with severe cases by year in Italy, the Netherlands, Norway, Spain, and Sweden, 1995-2014

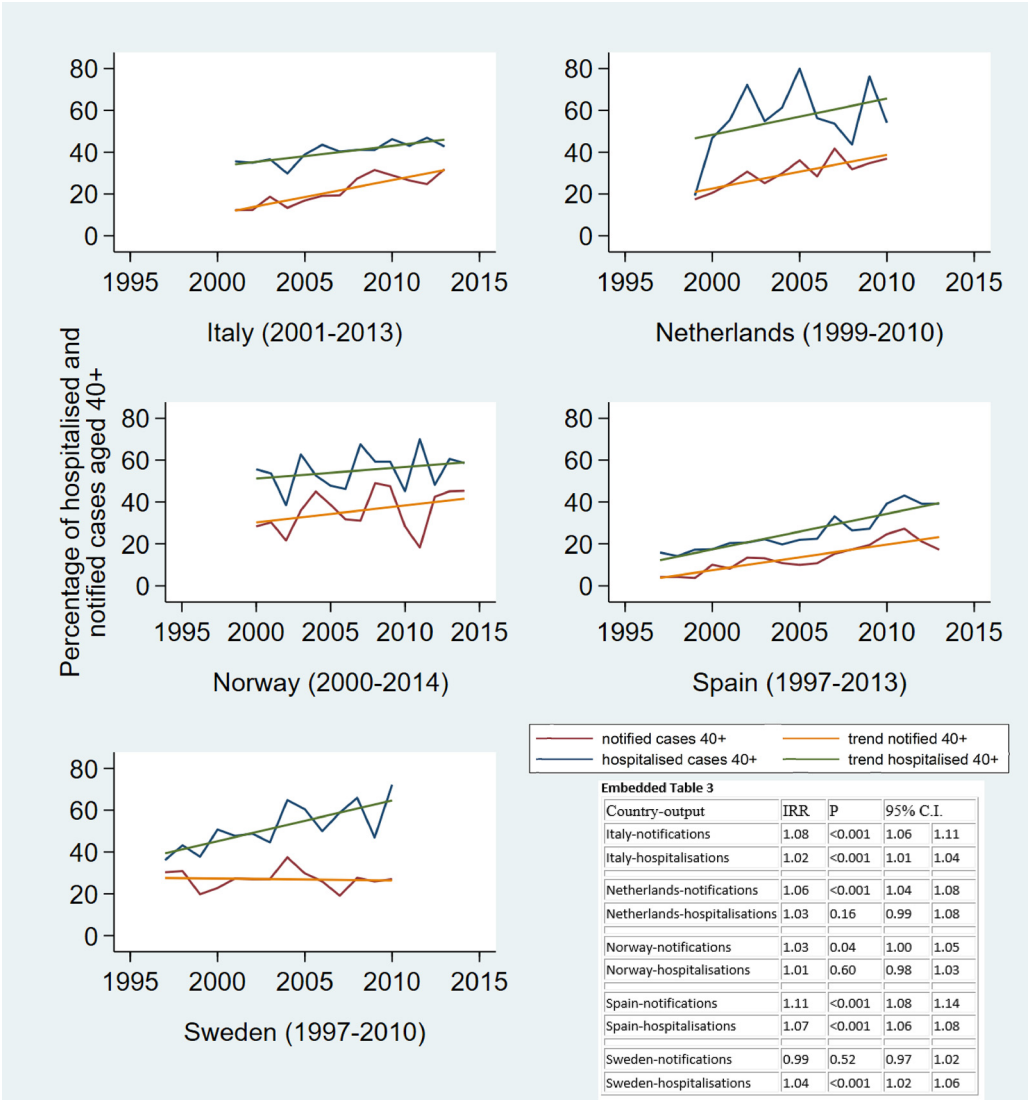
Country-output	IRR	P	95% C.I.	
Italy	0.98	<0.001	0.97	0.98
Netherlands	0.97	0.19	0.92	1.02
Norway	0.95	0.01	0.91	0.99
Spain	0.98	<0.001	0.97	0.99
Sweden	1.01	0.68	0.96	1.06

Proportion of severe hospitalisations

In all countries but Sweden, the proportion of severe hospitalisations decreased over the study period (Figure 3, embedded table 4). In Italy, Norway, and Spain, the decrease was from 2% to 5% per year and was statistically significant. A similar decrease of 3%, although not statistically significant, was observed in the Netherlands (P 0.19), whereas Sweden had a yearly increase of 1%, also not significant (P 0.68).

Risk factors for severe hospitalisation

In all countries, both in univariate and multivariable analyses, being ≥65 years of age was associated with an increased risk of severe hospitalisation when compared with patients aged 18-39 years (Table 5). When accounting for patients' age, comorbidities and year of hospitalisation, the increased risk for patients aged ≥65 years ranged from 1.2 in Italy to 3.1 in Sweden. Also, in Norway, Spain, and Sweden, patients aged between 40 and 64 years were at increased risk of severe hospitalisation compared with patients aged 18-39 years (increased risk ≈1.5), whereas in Italy, this age group had a 5% lower risk than the group aged 18-39 years (reference group).



Embedded Table 3

Country-output	IRR	P	95% C.I.	
Italy-notifications	1.08	<0.001	1.06	1.11
Italy-hospitalisations	1.02	<0.001	1.01	1.04
Netherlands-notifications	1.06	<0.001	1.04	1.08
Netherlands-hospitalisations	1.03	0.16	0.99	1.08
Norway-notifications	1.03	0.04	1.00	1.05
Norway-hospitalisations	1.01	0.60	0.98	1.03
Spain-notifications	1.11	<0.001	1.08	1.14
Spain-hospitalisations	1.07	<0.001	1.06	1.08
Sweden-notifications	0.99	0.52	0.97	1.02
Sweden-hospitalisations	1.04	<0.001	1.02	1.06

Figure 2. Proportion of notified and hospitalised patients with hepatitis A older than 40 years and corresponding trend lines over the study period in Italy, the Netherlands, Norway, Spain, and Sweden, 1995-2014

In the Netherlands, Spain, and Sweden, patients with comorbidity, particularly with liver disease, were found at increased risk of severe hospitalisation when compared with patients with no comorbidities. The risk in patients with liver disease other than HepA ranged from a 2-fold increase in the Netherlands to a 3-fold increase in Spain. In Italy, there was no significant difference.

The year of the hospitalisation was also associated with severe hospitalisation, with the risk of severe hospitalisation decreasing from 2% (in Italy) to 5% (in the Netherlands and Norway) every year. The variable sex was not included in the model as it was not associated with the outcome and had no effect on the other factor estimates.

Discussion

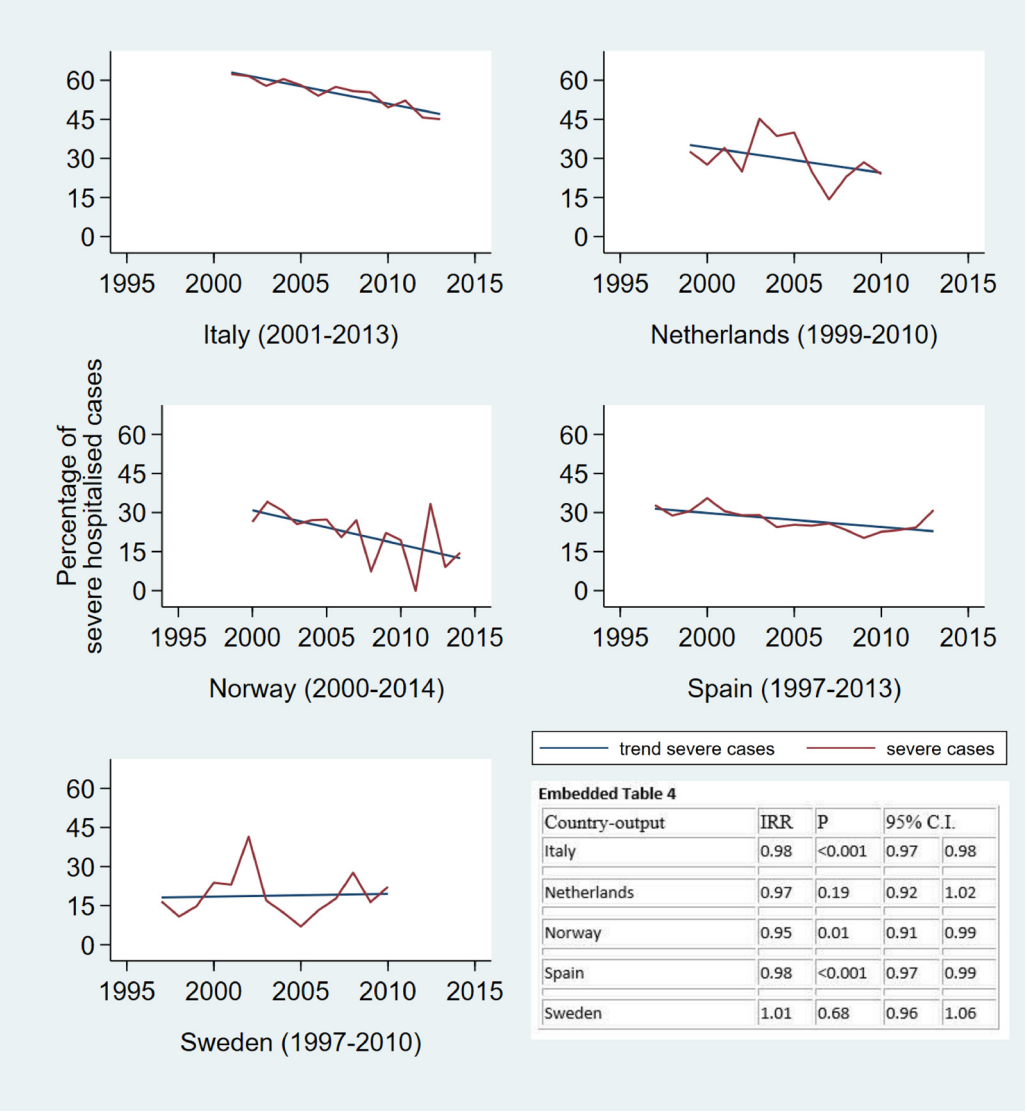
Our study analysed notifications and hospitalisations associated with HepA in selected EU/EEA countries to investigate possible changes in the severity of the clinical presentation of HepA hospitalisations between 1995 and 2014.

With some exceptions, our study results validated the study hypotheses. HepA notifications and hospitalisations decreased over time; the decrease of HepA notification rates was more pronounced than for HepA hospitalisation rates; the proportion of patients aged ≥40 years increased during the study period indicating an increase in the age at infection. There are a few deviations to note. In Spain, notification and hospitalisation rates were rather stable over time; of note, when excluding the 2 large outbreak years 2008-2009, the hospitalisation rate decreased slightly (IRR 0.99; P 0.03). In Italy, the Netherlands, Norway, and Sweden, notification rates decreased faster than hospitalisation rates, but overlapping CIs indicated that their trends were not significantly different. In Sweden, the proportion of notified patients aged ≥40 years slightly decreased over time.

In contrast, our analysis confuted the hypothesis that the proportion of severe HepA hospitalisations increased during the study period. All countries experienced lower proportions of severe cases in more recent years, although such a decrease was statistically significant only in Italy, Norway, and Spain.

The risk factor analysis for severe HepA clinical presentation confirmed that older patients, particularly if aged ≥65 years, and patients with comorbidities, particularly with liver diseases (except Italy), are more likely to have a severe outcome.

In the last decade, analyses of HepA hospitalisations have been performed in South Korea, Taiwan, and the United States



Embedded Table 4

Country-output	IRR	P	95% C.I.	
Italy	0.98	<0.001	0.97	0.98
Netherlands	0.97	0.19	0.92	1.02
Norway	0.95	0.01	0.91	0.99
Spain	0.98	<0.001	0.97	0.99
Sweden	1.01	0.68	0.96	1.06

Figure 3. Proportion of hospitalised patients with severe hepatitis A and corresponding trend lines over the study period in Italy, the Netherlands, Norway, Spain, and Sweden, 1995-2014

(Chen et al., 2016; Collier et al., 2014; Kim and Lee, 2010; Yoon et al., 2017). In contrast to our findings, the South Korean and the Taiwanese studies show increases either in the notification or in hospitalisation rates in recent decades. In contrast, Collier et al. present an analysis of the United States hospitalisation data with results comparable to the European setting: HepA hospitalisation rates declined significantly from 2000 to 2011, whereas the age and the proportion of comorbidities, particularly liver diseases, increased in patients that were hospitalised (Collier et al., 2014). The difference between the study results is not unexpected, as the historical and current HAV endemicity in the EU is more similar to the United States than to South Korea and Taiwan, which experienced a more recent epidemiological transition.

In addition to being, to our knowledge, the first European study analysing HepA hospitalisations, our main strengths are the extended period of observation and a large number of patients included, with most countries reporting quasi-100% coverage of at least public hospitals during the study period. The only exceptions were data on hospitalisations from the Netherlands, where overall coverage was just <80% owing to exclusion of hospitals with incomplete hospital registration data in some years, and the Spanish notifications, which were not available for the region of Catalonia. Furthermore, our study provides information on Nordic, Central and Mediterranean EU/EEA countries, where past HAV incidence and current susceptibility to HAV infection are rather different and are representative of most EU/EEA areas.

Amongst the main study limitations, we have to note that endemicity levels in Italy and Spain are less homogenous in geographical and historical terms than in the Netherlands, Norway, and Sweden (European Centre for Disease Prevention and Control, 2016). In addition, Apulia (Italy) and Catalonia (Spain) offer HepA vaccination to toddlers and adolescents since 1998, and Ceuta and Melilla since 2000 (Chironna et al., 2012; Dominguez et al., 2003; Godoy et al., 2018; Lopalco et al., 2008). The study results for Italy and Spain may therefore not apply to all the regions part of the 2 countries.

The Italian hospitalisation rate is surprisingly high, even higher than the same country notification rate. Having more HepA hospitalisations than notifications is conceptually challenging to explain. A significant underreporting affects the Infectious Diseases Routine Notification System in several Italian regions: the pattern of this underreporting is likely a complex mixture of factors, including reporting practices by physicians, as well as the operation of the surveillance system itself (Prato et al., 2004; Tosti et al., 2015).

Table 5
Univariate and multivariable negative binomial regression models for the risk factor of hospitalisation with severe hepatitis A, in Italy, the Netherlands, Norway, Spain, and Sweden, 1995-2014

Exposure		Crude IRR	P	95% CI	Adj IRR	P	95% CI
Italy							
Age-group	0-17	0.73	<0.001	0.69-0.78	**0.74**	**<0.001**	**0.70-0.78**
	18-39	Baseline					
	40-64	0.95	0.04	0.90-1.00	**0.95**	**0.02**	**0.91-0.99**
	65+	1.07	0.03	1.01-1.13	**1.06**	**0.04**	**1.00-1.12**
Comorbidities	no comorbidities	Baseline					
	liver disease	1.14	<0.001	1.07-1.22	1.04	0.16	0.98-1.10
	other comorbidities	1.04	0.13	0.99-1.10	0.96	0.08	0.92-1.00
Year		0.98	<0.001	0.97-0.99	**0.98**	**<0.001**	**0.97-0.98**
The Netherlands							
Age-group	0-17	0.59	0.15	0.29-1.20	0.61	0.18	0.30-1.25
	18-39	Baseline					
	40-64	1.62	0.03	1.06-2.49	1.49	0.08	0.96-2.30
	65+	2.24	0.001	1.37-3.66	**1.88**	**0.01**	**1.14-3.11**
Comorbidities	no comorbidities	Baseline					
	liver disease	2.53	<0.001	1.66-3.87	**2.08**	**0.001**	**1.34-3.23**
	other comorbidities	1.85	0.003	1.23-2.78	**1.64**	**0.02**	**1.08-2.50**
Year		0.97	0.19	0.92-1.02	**0.95**	**0.04**	**0.90-1.00**
Norway							
Age-group	0-17	0.64	0.34	0.30-1.34	0.65	0.26	0.31-1.37
	18-39	Baseline					
	40-64	1.52	0.06	0.99-2.35	**1.57**	**0.04**	**1.02-2.43**
	65+	2.72	<0.001	1.69-4.37	**2.69**	**<0.001**	**1.67-4.32**
Year		0.95	0.01	0.91-0.99	**0.95**	**0.02**	**0.92-0.99**
Spain							
Age-group	0-17	0.73	<0.001	0.62-0.85	**0.86**	**0.02**	**0.75-0.98**
	18-39	Baseline					
	40-64	1.44	<0.001	1.26-1.65	**1.39**	**<0.001**	**1.24-1.56**
	65+	2.34	<0.001	2.01-2.73	**2.10**	**<0.001**	**1.84-2.41**
Comorbidities	no comorbidities	Baseline					
	liver disease	3.15	<0.001	2.69-3.69	**2.58**	**<0.001**	**2.22-2.99**
	other comorbidities	2.2	<0.001	1.91-2.54	**1.80**	**<0.001**	**1.58-2.05**
Year		0.98	0.001	0.97-0.99	**0.96**	**<0.001**	**0.95-0.97**
Sweden							
Age-group	0-17	1.12	0.67	0.66-1.92	1.68	0.06	0.97-2.90
	18-39	Baseline					
	40-64	1.82	<0.01	1.25-2.66	**1.71**	**0.01**	**1.17-2.48**
	65+	3.49	<0.001	2.34-5.19	**3.10**	**<0.001**	**2.08-4.62**
Comorbidities	no comorbidities	Baseline					
	liver disease	3.48	<0.001	2.28-5.31	**2.91**	**<0.001**	**1.88-4.52**
	other comorbidities	3.11	<0.001	2.08-4.64	**2.52**	**<0.001**	**1.68-3.77**
Year		0.96	0.03	0.93-1.00	**0.96**	**0.01**	**0.93-0.99**

Abbreviations: CI = confidence interval; IRR = incidence risk ratio.

Regardless, the outputs of the Italian models are rather consistent with the models of the other countries and showed similar trends, which was reassuring. The risk factor analysis showed different results for Italy than the other countries: with Italian patients with comorbidities not being at a higher risk of a severe outcome. Such a deviation could reflect different attitudes toward hospitalisation in different countries. The same different attitudes toward hospitalisation could also be partially associated with the differences in hospitalisation length and frequency of re-hospitalisation in the different countries.

There were some limitations regarding data availability. Data for the Netherlands did not include information on liver transplantation. For Norway, we missed information on liver transplantation and comorbidities; also, multiple hospitalisations could be linked only for patients hospitalised in or after 2008. For Spain, it was only possible to link hospitalisations related to the same patient occurring in the same hospital and the 30 days after a previous discharge; because relapsing hepatitis can occur within 1 year from the first symptom onset, we may have missed linking a few hospitalisations associated with the same patient (re-admissions). Information on biomarkers of liver injury (e.g. liver transaminases) were unavailable for all countries. These missing data may have decreased the number of patients classified as “severe hospitalisations” and therefore underestimated the proportion of HAV admissions that had a severe outcome. However, for most of these missing data, we expect the bias to be constant over time, which would not influence the results of the trend and risk factor analyses.

Information on vaccination coverage, except for those regions offering universal childhood vaccination in Italy and Spain, is not available. Differences in vaccination coverage, along with the HAV susceptibility across age groups in the different countries, could help explain part of the differences identified in the frequency of notified and hospitalised cases in the different countries.

Similarly, linking hospitalisation and death registries was not feasible. Therefore, all patients who died owing to or with HepA at home shortly after the hospital discharge was not captured. This may have slightly underestimated the number of deaths and the overall number of severe outcome cases.

The lack of increase in the proportion of severe hospitalisations could be owing to the increasing cost of hospitalisations over the study period, or better management of admittances with consequent reduction of inappropriate admissions, especially in more recent years when many diagnostic and therapeutic procedures were transferred from hospital to ambulatory settings, resulting in shorter hospitalisations (Rosano et al., 2013). Non-HepA-specific hospitalisation data in EUROSTAT (https://ec.europa.eu/eurostat; database name “Certain infectious and parasitic diseases”) show differences in length of hospital stay in different EU/EEA countries,

and a decrease in the mean hospitalisation length from 2004 to 2014 (Eurostat, 2017). Because the length of the hospitalisation was the main driver in the definition of severe cases, we modelled the increase in the proportion of severe hospitalisations with only the "very severe hospitalisation" included as an outcome. We defined very severe hospitalisations as those patients having experienced at least 1 of the following conditions: death, liver transplant, hepatic coma, or ≥3 courses of hospitalisations with HepA. Thus, we excluded the length of the hospitalisation used for the definition of severe hospitalisation. Very severe hospitalisation could be defined only for Sweden and Spain. However, the model with very severe hospitalisations provided similar estimates to the model with severe hospitalisations, but without statistical significance owing to the lower power in this analysis (data not shown).

We also tested whether the age of patients with HepA increased over time by comparing patients aged ≥65 years to all younger patients. However, the results were like those previously presented.

Possibly, our study could have identified an increase in the severity of the HepA clinical presentation if performed in the same countries earlier, that is during or just after the transition from higher to lower endemicity (possibly from the 1970s to 2000s, or even earlier for the Nordic countries). Because some eastern EU countries have more recently experienced an intermediate HepA endemicity (Carrillo-Santisteve et al., 2017), colleagues in those countries may consider repeating this study to clarify whether they observe an increase in the severity of the clinical presentation of patients with HepA owing to their increasing age at infection. This could orientate prevention policies and reinforce the WHO recommendations on childhood vaccination in intermediate endemic countries (World Health Organization, 2012).

It is also possible that extending the study period until recent days could have slightly increased the trends in notification and hospitalisation rates, as it would include the large European outbreak disproportionally affecting MSM in 2016-2018 (Ndumbi et al., 2018). We should note, however, that the study period does include other large outbreaks (e.g. Sweden 1997-1998 [Nygård et al., 2001]; Norway 2004 [Blystad et al., 2004]; Spain 2008-2009 [Tortajada et al., 2009]) affecting 1 or more countries part of this analysis and that, as mentioned previously for Spain, these outbreaks are not bringing major changes to the notification and hospitalisation rates, or to the proportion of severe cases reported in this manuscript. The peaks in notifications, and to a lesser extent hospitalisations, associated with outbreaks have been largely absorbed by other the observations. In this regard, the 2013-2014 foodborne outbreak, which posed a large burden on Italy in 2013 (Severi et al., 2015), does not appear to have had an impact on the trends we report for this country. This might be different for the years 2017-2018, which had unprecedentedly high notification rates, particularly in Spanish and Italian males (European Centre for Disease Prevention and Control, 2022). In this regard, we should also consider that 2019-2020 were years with the lowest EU notification rates in available records (with the extremely low notification rates in 2020 most likely linked to the COVID-19 pandemic). In summary, including in our study, these recent outbreaks could have possibly slightly increased the trends in notification and hospitalisation rates, but we do not think this would bring a significant change in our results, and particularly not to the decrease in severe cases; thus making the results still valid as of January 2022.

In conclusion, our study made use of digitalised health information to confirm a decreasing trend in HepA hospitalisations and notifications, and increasing age at HepA infection, in representative countries of Nordic, Central, and Mediterranean Europe. Our study did not identify an increase in the severity of the clinical presentation of patients with HepA. Routine collection of additional hospitalisation-related information as biomarkers of liver injury could help make this and new analyses more targeted.

Our analysis of the risk factors associated with severe HepA clinical presentation confirmed that patients with liver diseases are at increased risk of severe diseases and could therefore be prioritised for vaccination, as recommended by the WHO (World Health Organization, 2012). Such a policy is already ongoing in several EU countries (European Centre for Disease Prevention and Control, 2016).

Our findings also provide a better understanding of the use of hospitalisations and clinical outcomes associated with the evolving HepA epidemiology in the EU/EEA during the last 2 decades. Our results can be of help to modellers and policymakers evaluating the current prevention policies in the EU/EEA population.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical Approval Statement

The study protocol (number 2015/1350-31) was approved by the Regional Ethics Review Board of Stockholm.

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