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REVIEW ARTICLE

Hepatitis A occurrence and outbreaks in Europe over the past two decades: A systematic review

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Abstract

Hepatitis A (HA) is a vaccine-preventable liver disease with >170 million new cases occurring yearly. In recent outbreaks in the USA, hospitalization and case-fatality ratios were >60% and ~1%, respectively. In Europe, endemicity persists and outbreaks continue to occur. We performed a systematic literature review to understand the changes in HA occurrence in Europe over the past two decades. PubMed and Embase were systematically searched for peer-reviewed articles published between 1 January 2001 and 14 April 2021 using terms covering HA, 11 selected European countries, outbreaks, outcomes and HA virus circulation. Here, we focus on HA occurrence and outbreaks in the five countries with the largest population and the most comprehensive vaccination recommendations: France, Germany, Italy, Spain and the UK; 118 reports included data for these five European countries. Notification rates ($\leq 9.7/100,000$ population) and percentages of men among cases ($\leq 83.0\%$) peaked in 2017. The number of person-to-person-transmitted cases and outbreaks decreased in children but increased in other risk groups, such as men who have sex with men (MSM). Sexually transmitted outbreaks in MSM clustered around 2017. Travel-related outbreaks were few; the proportion of travel-related cases decreased during the past two decades, while the number of domestic cases increased. Despite the existing risk-based vaccination recommendations, HA transmission shifted in proportions from travelers and children to other risk groups, such as MSM and older age groups. Because a substantial proportion of the European population is susceptible to HA, adherence to existing recommendations should be monitored more closely, and enhanced vaccination strategies should be considered.

KEYWORDS

food, men who have sex with men, travel, vaccine

Abbreviation: COVID-19, Coronavirus disease 2019; ECDC, European Centre for Disease Prevention and Control; ESCAIDE, European Scientific Conference on Applied Infectious Disease Epidemiology; HA, hepatitis A; HAV, hepatitis A virus; HIV+, human immunodeficiency-infected patients; MSM, men who have sex with men; n, number of patients/events; UK, United Kingdom; WHO World Health Organization

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1 | INTRODUCTION

Hepatitis A (HA) is a vaccine-preventable liver disease caused by a single-stranded ribonucleic acid virus (HAV). Infection may result in severe outcomes, especially at increasing ages and in older adults. HAV is resistant to low pH as well as heat and freezing temperatures and is mainly transmitted in common-source outbreaks (i.e. consumption of contaminated frozen food or water) or through close person-to-person contact via the fecal-oral route.¹ According to the Global Burden of Diseases, Injuries and Risk Factors Study,² >170 million clinical HA cases have been reported in 2017 worldwide, but the true number of infections and the disease burden are substantially underestimated due to underreporting and suboptimal surveillance systems. Asymptomatic or mild HAV infections, as well as low awareness among healthcare providers and misdiagnosis, may contribute to this.

According to the World Health Organization (WHO), up to 0.03% of HA cases are fatal.¹ Data published at the end of 2021 by the United States Centers for Disease Control and Prevention showed that in a series of HAV outbreaks ongoing since 2016, the case-fatality ratio was much higher, at nearly 1%. In addition, 61% of the >43,000 infected persons were hospitalized.³ These outbreaks also led to an increase in the HA notification rate by 294% between the 2013–2015 and 2016–2018 periods in the United States.⁴

Hepatitis A transmission is evolving worldwide, including in Europe, where endemicity persists and outbreaks continue to be reported.⁵ Traditionally, HAV transmission had been mostly attributable to travelers, who were at increased risk of exposure and infection when visiting higher endemic regions. However, during the Coronavirus disease 2019 (COVID-19) lockdown in Switzerland, when borders were closed and travel was at a standstill, the HA incidence decreased only by 5%, illustrating that a major proportion of cases is autochthonous (domestic) now.⁶ Recent outbreaks or increased infection rates in low-endemic settings have been associated with men who have sex with men (MSM), consumption of HAV-contaminated food (grown with contaminated water), drug use or homelessness.⁴ Water can be contaminated with feces from infected humans to spread HAV directly or indirectly. Contamination, especially of private wells, may result from sewage clogging/overflow or polluted stormwater runoff.⁷

We performed a systematic literature review to gain detailed insight over the published data on the occurrence, transmission patterns, severity and outcomes of HA in Europe in the past two decades. Considering endemicity, propensity of movement of people—including travelers, mass gatherings and immigration—surveillance systems and notification systems in place (see details in the Supplement S1), we selected 11 European countries for inclusion in this review. Here, we focus on disease occurrence data and the trends in transmission shift observed in five of these countries with the largest population size and the most comprehensive vaccination recommendations: France, Germany, Italy, Spain and the United Kingdom (UK). Because more rigorous HA prevention strategies could aid to achieve WHO's goal to eliminate viral hepatitis as a

public health threat by 2030,⁸ we also discuss current and potential vaccination strategies of HA in Europe.

A plain language summary contextualizing the relevance, the results and the impact of our study is described in [Figure S1](#).

2 | MATERIALS AND METHODS

PubMed was systematically searched for relevant peer-reviewed articles published in any language between 1 January 2001 and 14 April 2021. Search terms covered the disease (HA), the 11 selected countries, the term “outbreaks” and its synonyms, outcomes and terms for HAV circulation. A similar, complementary search was also performed in Embase for the same period. Additional details are presented in the Supplement S1.

The relevant articles retrieved from PubMed and Embase were selected using a three-step selection procedure. In the first step, titles and abstracts were screened by two researchers. Nonpertinent publication types (e.g. letters to the editor, editorials or comments) as well as seroprevalence and risk factor studies and studies in other than the selected countries were excluded. The full texts of articles meeting the inclusion criteria (relevant for the objectives, all ages, selected countries, prevalence of HAV in food/water/soil etc.) were subsequently screened. Additionally, full texts were also screened for articles for which title or abstract screening was inconclusive. In the data extraction phase, additional articles were excluded. If two or more articles presented similar results from identical datasets, only the most recent and complete was included. Articles about the same outbreak but different outcomes were combined in one row of the data extraction sheet. Reports on multi-country outbreaks were considered if any of the included countries had reported cases in the respective outbreak. Measures implemented to ensure quality control and reproducibility are detailed in the Supplement S1.

As part of the gray literature search, websites of the European Centre for Disease Prevention and Control (ECDC), ProMed, European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE) and national public health websites of the included countries were checked for additional relevant data published in the same period. Additional details are provided in the Supplement S1.

For all selected countries, notification of HA cases is passive, and for all except the UK, it is mandatory. [Figure 1](#) and [Table S1](#) detail whether the cases are reported by laboratories, physicians (including hospital physicians), hospitals and/or others, and what case definition is applied. Case definitions are detailed in the Supplement S1. Notification rates were extracted from the ECDC's Atlas for the 2007–2019 period and were complemented with data from peer-reviewed literature and national public health websites.

This review includes data on HA endemicity and outbreaks and focuses on the five largest European countries. Data for the remaining six selected countries included in the search are presented in the Supplement S1. Severity and outcomes of the disease in Europe in the past two decades will be summarized in a separate article.

FIGURE 1 Hepatitis A notification systems and case definitions.

Country	Data reported by				Case definition
	Laboratory	Physicians	Hospitals	Others	
France	✓	✓	✓	✓	Not specified
Germany	✓	✓	✓	✓	Other
Italy	✗	✓	✓	✗	Other
Spain	✗	✓	✓	✗	EU-2012
UK	✓	✗	✓	✗	EU-2012

UK: United Kingdom; Notification systems for all 11 selected countries and case definitions are described in the supplemental material

✓ Yes
✗ No

3 | RESULTS

3.1 | Search results

In PubMed and Embase, 134 peer-reviewed articles were found eligible for inclusion (Figure 2), of which 117 were outbreak reports, surveillance reports or case reports, and 17 were on HAV circulation in water or sewage. The gray literature search yielded 85 additional eligible reports, including peer-reviewed articles, annual or weekly reports of public health organizations, abstracts and news items. Of these 219 eligible reports, 169 contained data on the occurrence and transmission of HAV in the 11 selected European countries. One additional HAV outbreak report was found on ProMed-mail after the search. Of these 170 reports, 118 included data for at least one of the five largest European countries.

3.2 | Notification rates

Across the five largest European countries, <5 HA cases were notified per 100,000 population in most years between 2001 and 2020 (Figure 3A). Two peaks were observed concomitantly in several European countries, one in 2008–2009 and a higher one in 2017, the latter of which was more pronounced in Spain, Italy and France. The respective notification rates were 9.7, 6.2 and 5.1 per 100,000 population.

In 2017, a clearly distinguishable peak was also observed for the percentage of men among HA cases (Figure 3B, with details for each of the five largest countries in Figures S2–S6). In this year, the percentage of men among cases reported in the five included countries ranged between 66.7% in Germany and 83.0% in Italy. Although percentages were lower in other years of the 2001–2020 period, they were generally >50%, with a smaller peak observed in 2009 in Italy and Spain.

Earlier notification rate data were available for Spain. In the Catalonia region, where an HAV vaccination program in children (three-dose universal program) started in 1998, the notification rate declined from 5.51 per 100,000 person-years between 1992 and 1998 to 2.98 per 100,000 person-years between 1999 and

2005.⁹ In Valencia, the proportion of males was 65% between 1982 and 2003.¹⁰

The risk of HA in human immunodeficiency-infected (HIV+) patients was evaluated in two reports from France. In the first one, the estimated percentages of individuals who became infected with HAV during a half-year follow-up were 2.0%–3.8% among HIV+ MSM and 2.7%–3.0% among MSM pre-exposure prophylaxis users during a half-year follow-up.¹¹ In the second report, this percentage was 3.2% in HIV+ MSM or bisexual men during a one-year follow-up.¹²

3.3 | Outbreak reports

The time periods, impacted populations, numbers/ages of cases, proportions of males and routes of transmission in outbreaks published for the five European countries are summarized in Table 1 and Tables S2–S6.

Across outbreak reports limited to France, Germany, Italy, Spain or the UK, the main suspected transmission routes were close person-to-person contact ($n = 18$) and sexual transmission (MSM, $n = 17$), followed by consumption of contaminated food ($n = 13$), mixed (at least two transmission routes: person-to-person contact, sexual contact, food, travel and parenteral pathway; $n = 13$) and travel ($n = 3$) (Figure 4, Table 1). The transmission route was unclear or unknown for two outbreaks.^{13,14} Among all these reports, person-to-person-transmitted outbreaks were more frequent in the 1998–2008 period, all exclusively travel-related outbreaks were reported in the 2008–2010 period, the greatest number of foodborne outbreaks occurred in 2017, and MSM-transmitted outbreaks were more frequent in the 2016–2018 period (Figure 4).

3.3.1 | Foodborne outbreaks

The first foodborne outbreak in the period covered by our review was reported in Spain in 1999,¹⁵ where two other outbreaks were reported in 2005/2006 and 2017.^{16,17} Root causes were Coquina clams and razor shells. In Italy, the first of three was a

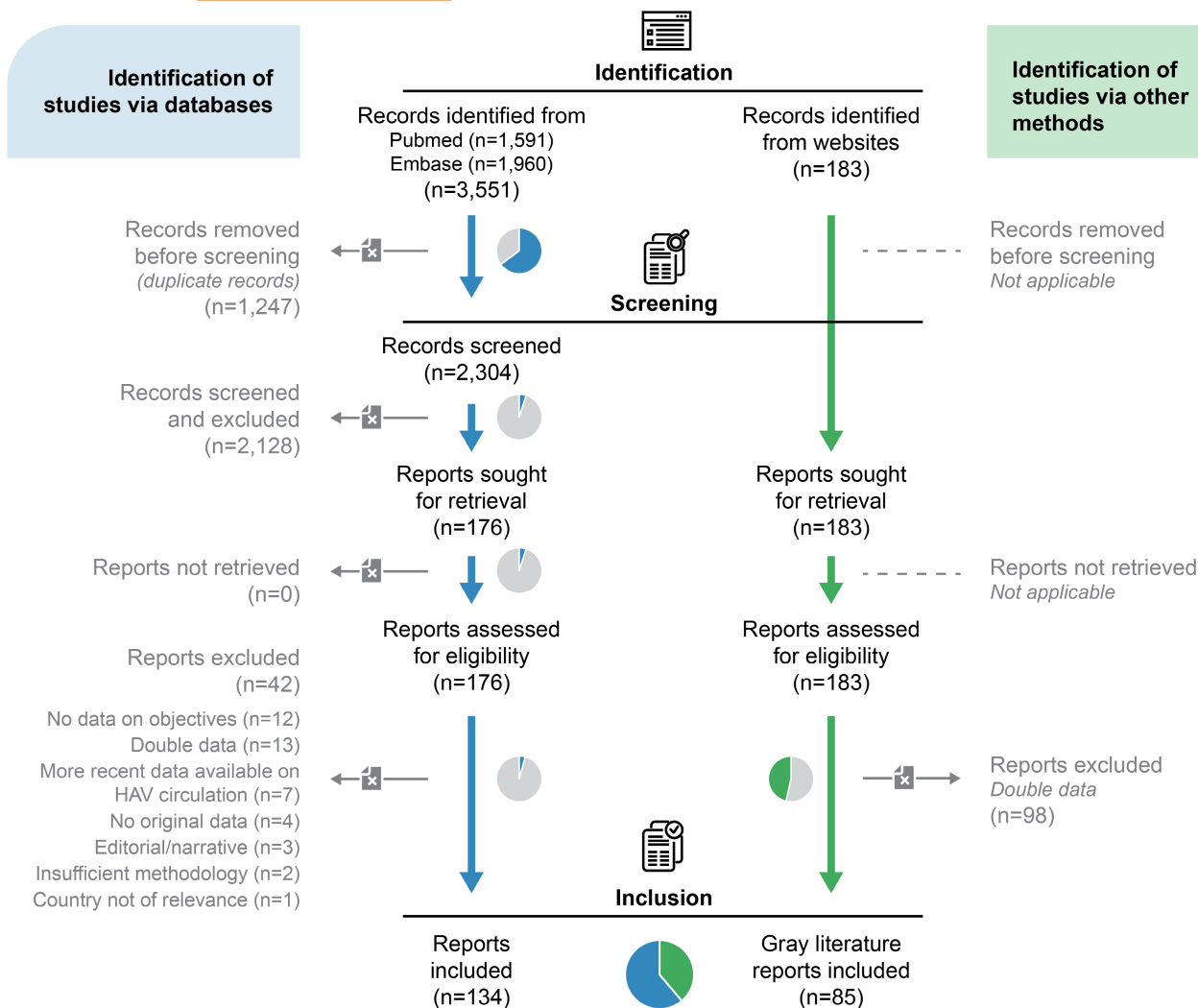


FIGURE 2 PRISMA flow diagram for the systematic literature review on hepatitis A occurrence and outbreaks in the 11 selected European countries based on peer-reviewed literature and gray literature. HAV, hepatitis A virus; n, number of reports.

smaller outbreak with delicatessen sandwiches as the possible transmission vehicle in 2002,^{18,19} while the two subsequent were much larger and caused by the consumption of raw shellfish in 2004²⁰ and of frozen berries in 2013/2014.²¹ In both France and Germany, two outbreaks occurred: in 2006/2007²² and 2017,²³ and in 2004²⁴ and 2017/2018,²⁵ respectively. Probable transmission vehicles were liver pate and bakery shop products in France and filled doughnuts and meat in Germany, with a strain originating from an MSM cluster identified in the latter.²⁵ Foodborne outbreaks in the UK were reported in 2011,²⁶ 2017²⁷ and 2019²⁸ and were due to semi-dried tomatoes, bakery products and canteen food, respectively. The additional report retrieved from ProMed-mail disclosed a foodborne (imported dates) outbreak that occurred in the UK in 2021, which affected a total of 31 persons of all ages.²⁹

A European multi-country outbreak likely caused by mixed frozen berries occurred between January 2013 and August 2014.³⁰ Most of the cases ($n = 1438$ [90%]) were reported from Italy and about 30 cases from Germany.

3.3.2 | Person-to-person-transmitted outbreaks

Person-to-person-transmitted outbreaks occurred between 1998 and 2006 in Germany^{31,32} and between 2000 and 2003 in Italy.^{33,34} All of them occurred in nursery or school settings or pediatric wards. In Spain, three outbreaks also occurred in school settings between 2002 and 2010,³⁵⁻³⁷ one occurred in the Roma population in 2004,³⁸ and three in preponderantly MSM populations in 2003/2004, 2016/2017 and 2016-2018.³⁹⁻⁴¹ In the UK, four outbreaks in nurseries or schools occurred at some point before 2006 and in 2008, 2012 and 2016.⁴²⁻⁴⁵ Person-to-person contact was also the main reported route of transmission in one outbreak in MSM in 2008/2009.⁴⁶

3.3.3 | Sexually transmitted outbreaks

Through 2015, three sexually transmitted outbreaks were reported in MSM across the five largest European countries: two in Spain in

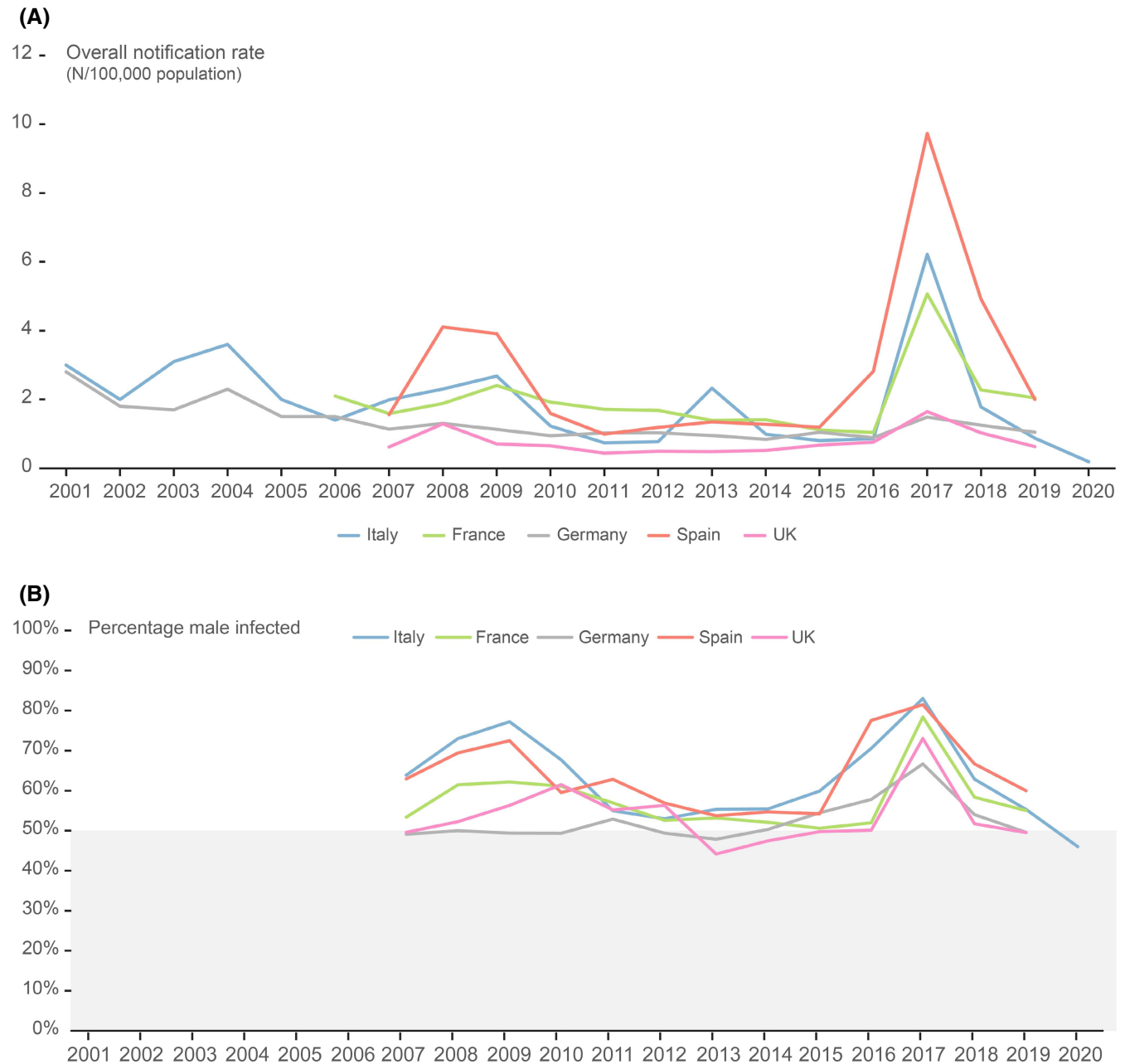


FIGURE 3 Notification rate of hepatitis A cases (A) and their proportion in men (B) in the five included countries from 2001 to 2020 (pending availability). N, number of cases; UK, United Kingdom. Additional details and data sources are presented in [Figures S2–S6](#).

2002 and 2008/2009,³⁹ and one in Italy between 2008 and 2010.⁴⁷ In 2016/2017, a European multi-country outbreak mainly affected MSM, with approximately 4100 cases.⁴⁸ The highest number of cases was recorded in Spain ($n = 2039$), followed by Italy ($n = 976$), France ($n = 750$) and Germany ($n = 668$). Cases were also reported from the UK among other European countries. The highest notification rate was also in Spain (4.4 per 100,000 population). Several national reports also covered this large outbreak. Sexually transmitted outbreaks in MSM were reported in 2016/2017 in France ($n = 2$),^{49,50} Italy ($n = 3$)^{51–53} and Spain ($n = 1$),⁵⁴ in 2016–2018 in Germany ($n = 1$),⁵⁵ Spain ($n = 1$)⁵⁶ and the UK ($n = 1$),⁵⁷ in 2017 in Italy ($n = 2$)^{58,59} and Spain ($n = 2$),^{60,61} and in 2017/2018 in Italy.⁶²

The index case was not reported in any of these sexually transmitted outbreaks.

3.3.4 | Mixed transmission outbreaks

Outbreaks with mixed transmission that occurred before the 2017 European outbreak that mostly affected MSM were reported in 1998/1999⁶³ and 2008⁶⁴ in the UK, in 2002/2003⁶⁵ and 2008/2009⁶⁶ in Italy, in 2012 in Germany⁶⁷ and Spain,⁶⁸ and in 2013/2014 in France.²³ A clustering of outbreaks with mixed transmission was seen in the 2017–2019 period, during which outbreaks

TABLE 1 Summary of national hepatitis A outbreak reports from the five included countries published in peer-reviewed literature and gray literature.

Country	Suspected main route of transmission	Reported period	Main population affected	Index case
France (n = 8)	Foodborne (n = 2)	2006/2007 2017	School children (n = 1) • Liver pate (n = 1) Visitors of restaurant (n = 1) • No specific food item identified (n = 1)	NA The cook
	Sexually (n = 2)	2016/2017	MSM (n = 2)	NR
	Travel (n = 1)	2008/2009	Travelers to Egypt (several sources possible) (n = 1)	NR
	Mixed (n = 3)	2007 2013/2014 2017	Tourists and locals (food and person-to-person) (n = 1) • Shellfish (n = 1) General (n = 1) • Bakery products and person-to-person (n = 1) MSM and general (sexually, person-to-person, food and travel) (n = 1)	NA Employee bakery NR
Germany (n = 9)	Foodborne (n = 2)	2004 2017/2018	General (n = 2) • Filled doughnuts (n = 1) • Butcher shop (n = 1)	NA Food-handler (MSM)
	Person-to-person (n = 3)	1998; 2004/2005 2006	Day-care and contacts (n = 2) Day-care/school and contacts (n = 1)	NR NR
	Sexually (n = 1)	2016–2018	MSM (n = 1)	NR
	Travel (n = 1)	2008	Travelers to Egypt (several food/water sources) (n = 1)	NR
	Mixed (n = 2)	2012 2018/2019	General (n = 2) • Bakery products and person-to-person (n = 1) • Frozen berries and person-to-person (n = 1)	NR NA
Italy (n = 18)	Foodborne (n = 3)	2002 2004 2013/2014	General (n = 3) • Sandwiches prepared in delicatessen (n = 1) • Raw shellfish (n = 1) • Frozen berries (n = 1)	Food-handler NA NA
	Person-to-person (n = 3)	2000 2002/2003	Pediatric ward (patients and staff) (n = 1) Day-care/school (n = 2)	Two children, NFS Child North African origin
	Sexually (n = 7)	2008/2010; 2016–2018	MSM (n = 7)	NR
	Mixed (n = 4)	2002/2003 2008/2009; 2017	IDU and general population (n = 1) • Raw shellfish (n = 1) MSM and general (n = 3)	NR NR
	Not clear (n = 1)	2014	Family (n = 1)	NR
Spain (n = 18)	Foodborne (n = 3)	1999 2005/2006 2017	General (n = 2) • Coquina clams (n = 1) • Razor shells (n = 1) Visitors/employees of restaurant (n = 1)	NA NA Employee NFS
	Person-to-person (n = 7)	2002/2003; 2010 2003/2004; 2016/2017 2004 2005/2006 2016–2018	Day-care (n = 2) MSM (MSM but no data on sexual activity) (n = 2) Roma (n = 1) School children (n = 1) MSM and general (n = 1)	NR; father of asymptomatic child NR NR NR NR
	Sexually (n = 6)	2002; 2008/2009; 2016–2018	MSM (n = 6)	NR
	Mixed (n = 2)	2012 2017	Children; one adult (travel and person-to-person) (n = 1) General (n = 1) • Bakery products and person-to-person (n = 1)	NR Food-handler (MSM)

TABLE 1 (Continued)

Country	Suspected main route of transmission	Reported period	Main population affected	Index case
United Kingdom (<i>n</i> = 13)	Foodborne (<i>n</i> = 3)	2011 2017 2019	General (<i>n</i> = 3) • Semi-dried tomatoes (<i>n</i> = 1) • Bakery products (<i>n</i> = 1) • Food in school canteen (<i>n</i> = 1)	
	Person-to-person (<i>n</i> = 5)	NR; 2008; 2016 2008/2009 2012	School children and contacts (<i>n</i> = 3) MSM (MSM but no data on sexual activity) (<i>n</i> = 1) Nursery (<i>n</i> = 1)	NR NR Travel to Zimbabwe
	Sexually (<i>n</i> = 1)	2016–2018	MSM (<i>n</i> = 1)	
	Mixed (<i>n</i> = 2)	1998/1999 2008	IDU (person-to-person and parenteral) (<i>n</i> = 1) Six families (travel and person-to-person) (<i>n</i> = 1)	NR Travel to Pakistan
	Not reported (<i>n</i> = 1)	2000	IDU, homeless and contacts (<i>n</i> = 1)	NR
	Travel (<i>n</i> = 1)	2010	Orthodox Jewish people (<i>n</i> = 1)	Travel to Israel

Note: Additional details and data sources are presented in Tables S2–S6.

Abbreviations: IDU, injecting drug users; MSM, men who have sex with men; *n*, number of reports; NA, not applicable; NFS, not further specified; NR, not recorded.

occurred in 2017 in France (*n* = 1),⁶⁹ Italy (*n* = 2)^{70,71} and Spain (*n* = 1),⁷² and in 2018/2019 in Germany.⁷³

3.3.5 | Travel-related outbreaks

National reports from the five largest European countries described HA outbreaks in travelers returning from Egypt to Germany in 2008,⁷⁴ and to France in 2008/2009,⁷⁵ and in individuals returning from Israel to the UK in 2010.⁷⁶

Between November 2012 and April 2013, 104 confirmed and probable cases were reported in individuals traveling from Egypt to 14 European countries including France, Germany and the UK. Most cases were from Germany. No further details on the source of infection were provided.⁷⁷ From January to June 2018, 103 cases were reported in individuals traveling from Morocco to seven European countries, including France, Germany, Spain and the UK.⁷⁸

3.4 | Surveillance studies—transmission routes and risk factors

Aside from the outbreak reports described in the previous section, surveillance studies have also been identified by our literature review. In France, the main route of HAV transmission during the 2006–2015 period was close person-to-person contact (46%) and travel abroad (38%).⁷⁹ In 2018, there was an increase in number of cases returning from Morocco, which decreased slightly in 2019.⁸⁰

In Germany, the percentages of travel-related cases were 39% in 2001⁸¹ and 34% in 2019.⁸² Between September 2015 and March 2016, almost 40% of HA cases occurred due to person-to-person transmission among asylum seekers.⁸³

In Italy, the most frequent risk factors for HA during the 1991–2006 period were food-related (shellfish consumption, 66%) and travel to more highly endemic areas (18%).⁸⁴ Shellfish consumption

(85%) and travel outside the region or outside Italy (26%) were also the most frequent risk factors in Puglia in 2008/2009, after 10 years of universal pediatric HA vaccination.⁸⁵ In 2010, seafood consumption accounted for 70% of the HAV cases in Campania.⁸⁶ Of the hospitalized cases that occurred between 2016 and 2017 in Rome (*n* = 141), 70.2% reported sexual encounters as the most probable risk factor and 7.8% reported consumption of raw shellfish.⁸⁷ In 2017, 2018 and 2019, seafood and MSM contacts were the most common routes of transmission.^{88–90}

In Spain, only few of the up to 211 annual outbreaks that occurred between 2012 and 2018 were waterborne or foodborne. In 2017 and 2018, >50% of the outbreaks were due to person-to-person transmission. Only few outbreaks were travel-related.^{91–96} In Catalonia, following the introduction of the HA and hepatitis B vaccination programme for 12-year-olds in 1998, most cases that occurred between 2005 and 2015 were travel-related (24.6%) or transmitted from person-to-person (20.1%).⁹⁷ Between the 1991–1998 and 2000–2012 periods (pre- and postvaccination), the number of person-to-person outbreaks originating from schools decreased, but outbreaks originating from MSM or immigrants increased.⁹⁸ The rate of cases associated with outbreaks was higher in the prevaccination compared with the postvaccination period.⁹⁹ In Cantabria, the proportion of MSM-transmitted cases increased from January 2013–May 2016 to June 2016–September 2018.⁵⁶ In Guadalajara, the most common route of transmission between 1991 and 1999 was person-to person contact (59.4%) followed by travel (7.9%).¹⁰⁰ Person-to-person contact was also the most frequent transmission route in 2004–2009 in Valencia.¹⁰¹ Of the cases hospitalized in Madrid between January 2005 and May 2017, 71.9% were in men and 20.5% were travel-related.¹⁰² In Andalusia, both peaks in notification rates, in 2008/2009 and 2016/2017, were related to MSM.¹⁰³

In England, of the 19 identified outbreaks (55 confirmed cases) during April 2011–April 2015, 13 (68%) occurred in an educational setting (school/nursery), four in households, one in a care home

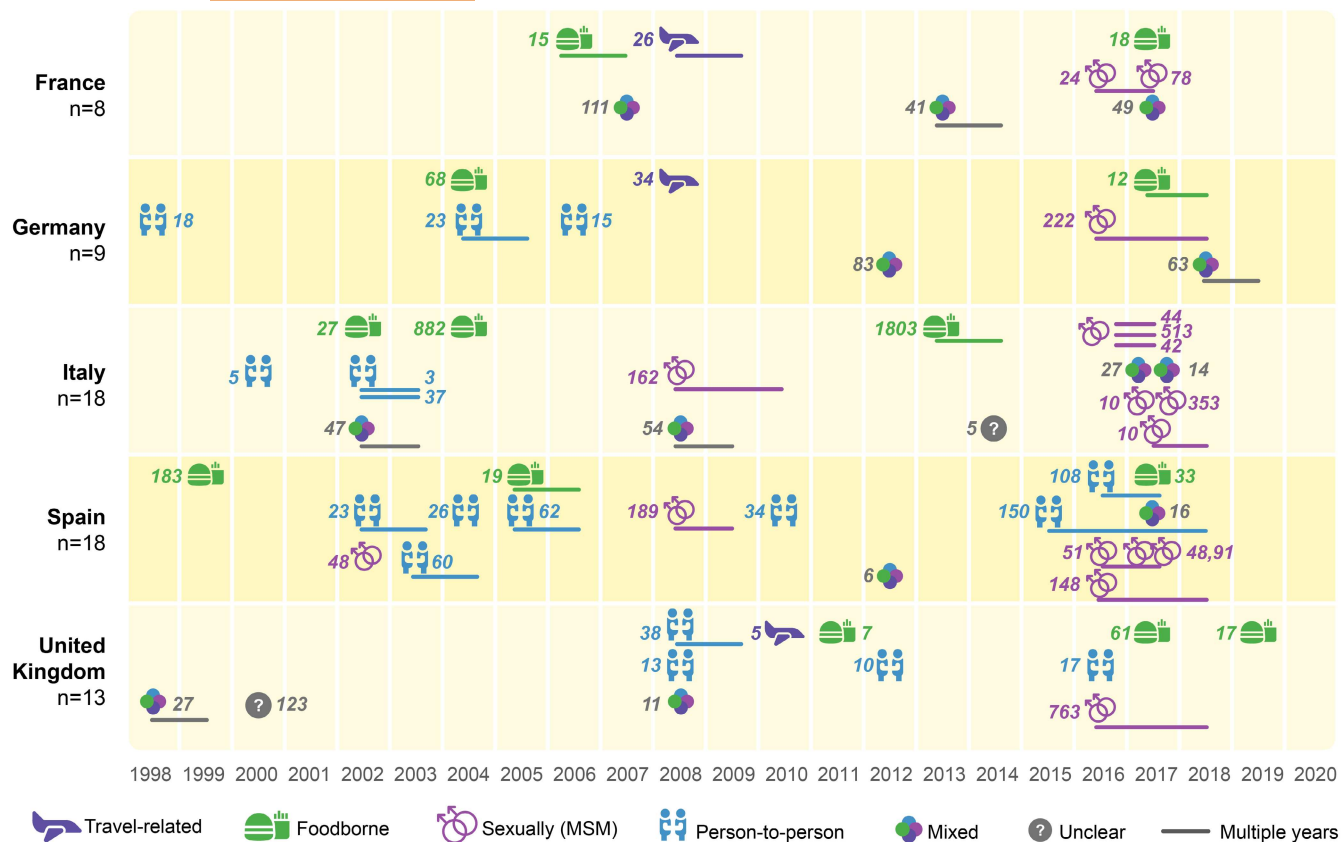


FIGURE 4 Suspected main route of transmission in national hepatitis A outbreak reports from France, Germany, Italy, Spain and the UK. MSM, men who have sex with men; n, number of outbreaks; UK, United Kingdom. Numbers denote total cases in each outbreak. Additional details and data sources are presented in [Tables S2–S6](#).

facility and one during a choir trip.¹⁰⁴ Between 2009 and 2019, 0.3%–7.8% of the cases were travel-related.¹⁰⁵

One report describes travel-related cases that occurred in multiple European countries between 2009 and 2015.¹⁰⁶ In France and Germany, respectively, 43.1% and 37.1% of these occurred in persons <15 years.¹⁰⁶

3.5 | HAV circulation in water/sewage

In France, no HAV was found in water samples collected in the Seine through Paris between 2013 and 2014,¹⁰⁷ but almost all wastewater samples in an urban area in Central France were positive for HAV.¹⁰⁸

In Germany, the two studies from the early 2000s showed that HAV was circulating in water samples.^{109,110} In Greece, HAV was found in untreated sewage in Patras between November 2007 and July 2009,¹¹¹ and once in a harbor in June 2013.¹¹² Other samples did not contain HAV.^{112,113} In two of the seven studies from Italy, no HAV was found in water/wells.^{114,115} In the other five studies, positive samples were found,^{116–120} with sometimes high proportions of samples contaminated with HAV, for example up to ~30% of sewage samples in the Campania region between 2015 and 2018.¹¹⁷ Both

studies from Spain showed HAV circulation in water and sewage samples.^{121,122}

3.6 | Case-fatality rates

The case-fatality rate for HAV reported in the included studies was generally low. Over the study period, deaths during outbreaks were reported in five countries: Spain, Denmark, Germany, Hungary and Italy; with a case-fatality rate between 0.05% and 0.26%.^{84,123–133} In four other countries (France, Sweden, Switzerland and the UK), no deaths were reported in the ECDC's Atlas,¹²³ in the included outbreak studies or in the gray literature.^{80,105,134–136} However, for the two latter sources, it is not clear whether deaths did indeed not occur, or whether data were missing. No deaths were reported in Greece¹³⁷ and the Netherlands.¹³⁸

Although this systematic literature review did not focus on the risk factors for death, any underlying conditions in fatal cases included in outbreak reports were collected. These underlying conditions were pre-existing liver diseases (such as hepatitis B or hepatitis C infection), HIV infection, renal failure, diabetes, intravenous drug use, pulmonary neoplasia, pulmonary edema and other unspecified

conditions.^{14,65,84,124,125,139–141} About 70% of the fatal cases were encountered in persons aged ≥ 60 years old.^{14,65,78,84,124,125,142}

4 | DISCUSSION

Hepatitis A virus transmission patterns and impacted populations have changed in Europe during the past two decades. Consistent with this finding, other regions have also witnessed a change in HAV occurrence in the recent past,¹ suggesting that prevention strategies may need to be enhanced.

The age of individuals affected by HAV outbreaks has increased, and populations at risk of HAV infection have changed. While outbreaks with person-to-person transmission occurred mainly in nursery and school settings between 1998 and 2010, the past decade witnessed a shift in the population affected by person-to-person-transmitted outbreaks to other populations, such as MSM. This is partly because in some outbreaks in MSM from the past decade the main reported transmission route was close person-to-person rather than sexual. However, most sexually transmitted outbreaks in MSM occurred around 2017, as confirmed at both European level and in national outbreak reports. This large multinational outbreak was also reflected in the notification rates across European countries during the same period. The occurrence of outbreaks with mixed and food-borne transmission in the same period reflected how HAV transmission can branch to other populations of all ages in such scenarios.

Travel-related HAV infections are imported by individuals traveling to regions with higher HAV endemicity who tend to spread the disease domestically after returning from their journey. Surveillance studies showed that the number of domestically acquired HAV cases tended to increase, and the proportion of travel-related cases tended to decrease during the past two decades. In addition, available data indicated that all of the relatively few travel-related outbreaks occurred due to imported cases from Egypt, Israel or Morocco. In line with our findings, data from the ECDC show that the proportion of travel-related cases in the European Union/European Economic Area countries decreased from 52.8% in 2007 to 8.6% in 2020,¹²³ partly due to the impact of travel restrictions during the COVID-19 pandemic. Corroborated with the stable trend in HA case notifications across Europe in periods without major outbreaks, this reduction confirms the increased incidence in other risk groups. Finally, when comparing the ~2000–2010 and ~2010–2020 periods, the numbers of individuals per outbreak tended to increase regardless of transmission route. Also considering the above-mentioned trend in HA case notifications across Europe, the increasing size of outbreaks implies a decreasing number of isolated cases.

Prevention strategies against HA include improved sanitation, food safety and immunization. Worldwide, several HA vaccines with well-established safety profiles are licensed from the age of 1 year and are highly effective in preventing the disease.¹⁴³

Pediatric vaccination programs against infectious diseases offer both direct protection in vaccinated children and indirect protection in other unvaccinated age groups. Only a few European countries/

regions with low/very low seroprevalence recommend or provide universal HA vaccination in children. While Greece, Catalonia (Spain) and Puglia (Italy) have publicly funded universal HA vaccination programs, in Poland, the Czech Republic and Cyprus, vaccination is recommended but not publicly funded.¹⁴⁴ In Catalonia, universal pediatric HA vaccination led to a reduction in person-to-person-transmitted outbreaks originating from schools. However, outbreaks originating from MSM or immigrants increased between the pre- and postvaccination periods,⁹⁸ underscoring the limitations of pediatric vaccination programs.

All of the five largest European countries have vaccination recommendations for adult risk groups and travelers to endemic areas. Common risk groups include chronic liver disease patients and MSM, but additional risk groups are not harmonized and differ across these countries (Figure 5). Yet, what is lacking is an understanding of how well the recommendations are implemented as these are not systematically tracked, and coverage data are scarce-to-non-existent, standing in stark contrast with other vaccine-preventable diseases such as hepatitis B or COVID-19.^{145,146} Our data showed that a large proportion of the notified HA cases and many recent outbreaks had an impact on populations at risk, suggesting that there is a need to improve adherence to national-level recommendations and vaccination coverage. Since the entire previously unvaccinated or uninfected general population is at risk of HA, HAV has a strong potential to cause large outbreaks with potentially serious consequences,³ especially in populations in which the seroprevalence is low. Taken together with the high number of infections transmitted person-to-person or by food, including previously unsuspected domestic food chains, risk-based recommendations may be insufficient to protect all vulnerable adults, including the general population, against HA infection and outbreaks.

The data reviewed herein have certain limitations. Due to the high degree of underreporting, the true HA occurrence is likely higher than the occurrence of reported cases. Certain outbreaks were likely not identified by our literature review due to publication gaps. Furthermore, the source of the outbreak was unknown or not reported in some publications. Due to variations in case definitions, any potential differences between countries should be interpreted with caution.

The transmission patterns of HA have changed during the past two decades in European countries, with a shift in proportions from travelers and children to other risk groups such as MSM and older age groups, though cases also included the general population. Despite the availability of cost-effective vaccines against HA, the number and size of outbreaks have increased in the past decade, even in populations in which vaccination is consistently recommended across Europe. This illustrates that—as experienced previously with hepatitis B—risk-based recommendations are a suboptimal solution.¹⁴⁷ Because the seroprevalence is low in most European countries, substantial proportions of the population are vulnerable to HAV infections and associated complications. Vaccination coverage is untracked in risk groups and therefore unclear, and recommendations are heterogeneous across countries. Hence, there is a need to

Risk Group	France	Germany	Italy	Spain	UK
Chronic liver disease	✓	✓	✓	✓	✓
Haemophilia		✓	✓ ^a		✓
Men who have sex with men	✓	✓ ^b	✓	✓ ^c	✓
Drug addicts			✓	✓	✓
Cystic fibrosis	✓				
Children up to 6 years of age			✓		
Children of immigrants travelling to endemic areas			✓		
Contacts of adopted children				✓	
Lab workers			✓	✓	✓
Staff of residential institutions	✓ ^d	✓ ^e			✓
Sewage workers	✓	✓			✓
People who work with primates			✓	✓	✓
Food packager/handlers	✓				✓ ^f
Staff in day care centres		✓			✓ ^f

a: Coagulopathies requiring long-term therapy; **b:** And persons with sexual behaviour which increases exposure risk; **c:** And sex workers; **d:** Young people in institutions for children with disabilities; **e:** Residents of psychiatric institutions or facilities for behavioural disorders/ cerebral damage, Sheltered employment facilities, Children's homes, Asylum seekers' shelters; **f:** During outbreaks

FIGURE 5 Vaccination recommendations in France, Germany, Italy, Spain and the UK. UK, United Kingdom.

improve monitoring of the disease burden and vaccination coverage, as it has been done for hepatitis B. The extent of implementation and effectiveness of current programs need to be better understood, healthcare providers and their patients need to be better informed, and existing vaccination recommendations in European countries need to be enhanced to reduce HAV transmission and endemicity. This would aid in achieving WHO's goal to eliminate viral hepatitis as a global health threat by 2030.⁸ Adult vaccination is set to become the standard of care, and the timely evaluation of the impact of existing HA vaccination programs would facilitate establishing future national policies.

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CONFLICT OF INTEREST STATEMENT

AA and PM are employees of GSK, declare financial and non-financial relationships and activities, and hold shares as part of their employee remuneration. The institution of EB and JE received grants and payment from GSK for developing this study. EB and JE also report grants from GSK for other projects. PVD declares that the University of Antwerp obtains grants from vaccine manufacturers

(including GSK) for the conduct of vaccine trials. RS, GK and KM declare no conflicts of interest relating to the subject presented here.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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