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Hantavirus infections in Italy: not reported doesn't mean inexistent

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Abstract. *Background:* Hantaviruses can cause serious human diseases including hemorrhagic fever with renal syndrome (HFRS) and Hantavirus Cardiopulmonary Syndrome (HCPS). European Hantavirus are usually associated with HFRS, and their geographical distribution mirrors the ecology of reservoir host species. Epidemiology of HFRS is well-studied in Western Europe, but data from Italy are fragmentary. *Methods:* We searched into two different databases (PubMed and EMBASE), focusing on studies reporting the prevalence of Hantaviruses in Italy. Data were extracted using a standardized assessment form, and results of the analyses were systematically reported, summarized and compared. *Results:* We identified a total of 18 articles, including 12 reports (total population: 5,336 subjects, 1981-2019) and 6 case reports (1984-2019). In total, 200 subjects exhibited some degree of seropositivity, with a pooled seroprevalence of 1.7% (95% confidence interval 0.7%-4.0%) in the general population. Higher occurrence was reported in selected subgroups, i.e. acute (28.7%, 95%CI 22.1-36.2) and chronic (6.6%, 95%CI 4.7-9.1) renal failure, forestry workers (3.0%, 95%CI 1.4-6.5, actual range 0.0 to 10.8%). *Conclusions:* In the last decade, no human cases of hantavirus infection have been officially reported in Italy. However, our analysis stresses the actual occurrence of Hantavirus among general population and in selected population groups. Further studies on hantavirus infection rates in reservoir host species (rodents, shrews, and bats) and virus transmission to humans are needed to prevent outbreaks in the future.

Key words: Epidemiology, Hemorrhagic fever with renal syndrome, Hantavirus disease, Outbreaks, Rodents, Western Europe; Italy.

Introduction

Hantaviruses (family *Hantaviridae*) are monopartite, trisegmented, negative-stranded enveloped RNA viruses belonging to the of the order of *Bunyavirales* (1–3). To date, 28 species of Hantaviruses have been recognized worldwide, being usually dichotomized in Old World or Eurasian and New World or American species (1,4,5). Heterogeneity of hantaviruses is a consequence of the strictly coevolution with their hosts, mainly rodents and insectivores (3), but also chiropters, and even reptiles and fishes (6), whose geographical distribution mirrors that of the pathogens (1).

Human infections usually occur through inhalation of aerosols including excreta of the hosts (i.e. urine, feces, saliva), or more rarely by their bites (1–3).

On the contrary, inter-human spreading is possible but unlikely, having been reported only for some strains of the Andes virus (1). Therefore, the main risk factor for Hantavirus infection is represented by occupations that favor human-rodent contact, including forestry workers, farmers, and military personnel (1).

Human Hantavirus infections share a common pathway, with initial invasion of endothelial, epithelial, dendritic, and lymphocyte cells that elicit increased vascular permeability and acute thrombocytopenia, with potential impairment of micro-vascular beds (1). The large majority of human infections occurs mostly unnoticed, either asymptomatic or as a mild flu-like syndrome characterized by high fever, malaise, and myalgia. However, a variable share of all cases develops severe systemic disorders, whose clinical presentation varies according to the viral strains prevalence (2), with mortality rates ranging from 12% to 30% (1,2). For example, East Asian (e.g. Hantan virus and Seoul virus) and the European Dobrava-Belgrade virus (DOBV) usually cause renal failure and hemorrhagic manifestations varying from petechiae to internal bleedings (Hemorrhagic Fever with Renal Syndrome, HFRS), with a case fatality rate up to 15% (4,7). The most frequently reported European Hantavirus, the Puumala virus (PUUV) usually causes a milder form of HFRS, i.e. nephropathia epidemica (NE), which is generally not associated with major hemorrhagic symptoms and has a low case fatality rate of approximately 0.4% (7). With 100,000 to 200,000 incident cases every year, HFRS largely exceeds the burden of disease associated with American Hantaviruses such as the Andes virus (ANDV), and the Sin Nombre virus (SNV). On the other hand, New World Hantaviruses usually cause a more severe syndrome characterized by pneumonia and cardiopulmonary disfunction (i.e. Hantavirus Cardiopulmonary Syndrome, or HCPS), whose case fatality rate that may range up to 40%.

The majority of all human Hantavirus infections occurs in Mainland China as HFRS, with an average annual incidence of 0.83/100,000 inhabitants (2), but also European Region is severely affected, with a total disease burden ranging between 9,000 to 15,000 cases/year, mostly associated with PUUV infection. According to European Centre for Disease Prevention and Control (ECDC), epidemiology of Hantavirus infections is quite heterogeneous: between 2011 and 2018, in most of Central and Eastern European Countries the incidence ranged from 0.4 to 1.1 cases/100,000 persons, while no cases have been officially reported in Southern countries such as Spain, Portugal, and Italy.

Despite its proximity to endemic countries, and the availability of earlier reports on suspected NE/HRFS (1,8–15), to date no autochthonous Italian cases have been officially reported. Our study will therefore attempt to:

Identify the published measurement of Hantavirus seroprevalence in Italy;

Ascertain geographic heterogeneity, and reconcile possible variation in Hantavirus seroprevalence rates with occupational exposure.

Materials and Methods

This systematic review has been conducted following the PRISMA (Prepared Items for Systematic Reviews and Meta-Analysis) guidelines (16). We searched conventional scientific databases (i.e. PubMed and EMBASE) for relevant studies until 31/08/2020, without any chronological restriction. The search strategy was a combination of the following keywords (free text and Medical Subject Heading (MeSH) terms): ("*Hantavirus disease**" OR "*Hantavirus Cardiopulmonary Syndrome*" OR "*HCPS*" OR "*Hemorrhagic Fever with Renal Syndrome*" OR "*HFRS*" OR "*Nephropathia epidemica*") AND («*Italy*» OR «*Italian*») AND («*epidemiology*» OR «*prevalence*» OR «*frequency*» OR «*occurrence*») (**Figure 1**). Records were handled using a references management software (Mendeley Desktop Version 1.19.5, Mendeley Ltd 2019), and duplicates were removed.

Documents eligible for review were original research publications available online or through inter-library loan. Articles had to be written in Italian, English, German, French or Spanish, the languages spoken by the investigators. Studies included were national and international reports, case studies, cohort studies, case-control studies and cross-sectional studies. Only article reporting on humans, and including the raw number of prevalent cases, or crude prevalence rates, were eligible for the full review. Retrieved

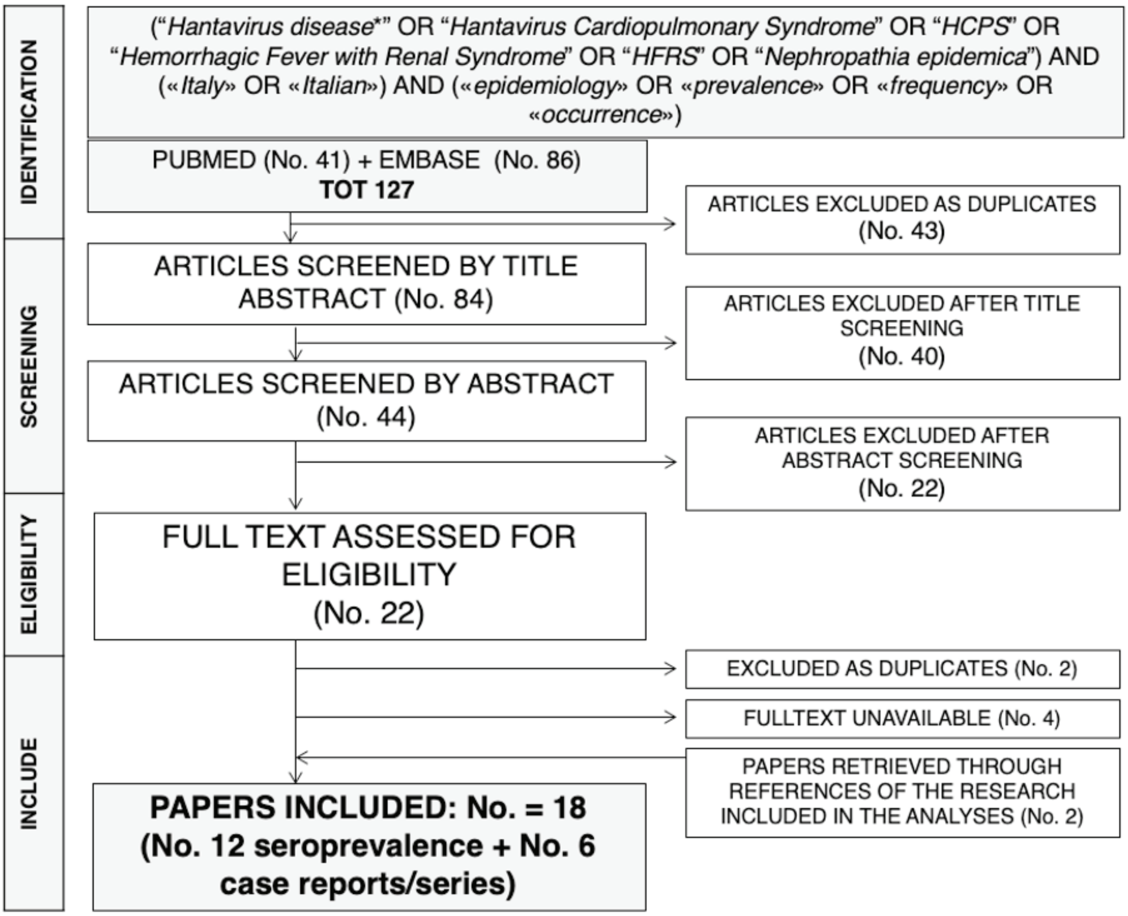


Figure 1. PRISMA flow diagram including keywords employed for the inquiry, including ("*Hantavirus disease**" OR "*Hantavirus Cardiopulmonary Syndrome*" OR "*HCPS*" OR "*Hemorrhagic Fever with Renal Syndrome*" OR "*HFRS*" OR "*Nephropathia epidemica*") AND («*Italy*» OR «*Italian*») AND («*epidemiology*» OR «*prevalence*» OR «*frequency*» OR «*occurrence*»).

documents were excluded if: (1) full text was not available; (2) articles were written in a language not understood by reviewers; (3) reports lacked significant timeframe (i.e. the prevalence year); (4) reports lacked definition of the geographical settings, or it was only vaguely defined.

Two independent reviewers reviewed titles, abstracts, and articles. Titles were screened for relevance to the subject. Any articles reporting original studies, which did not meet one or more of the exclusion criteria, were retained for full-text review. The investigators independently read full-text versions of eligible articles. Disagreements were resolved by consensus between the two reviewers; where they did not reach consensus, input from a third investigator (MR) was obtained. Further studies were retrieved from reference lists of relevant articles and consultation with experts in the field.

Data abstracted included:

1. Settings of the study: prevalence year, Italian region;
2. Occupational settings of the sampled cases (if available);
3. Total number of prevalent cases;
4. Number of reference population.

We first performed a descriptive analysis to report the characteristics of the included studies. Crude prevalence figures were initially calculated: if a study did not include raw data, either as number of prevalent cases, or referent population, such figures were reverse-calculated from available data. In cases of studies dealing with the very same population in various point of time, estimates were calculated for the more recent study by removing cases previously included in earlier reports.

Pooled prevalence (as prevalent cases/100 population) estimates were then calculated by means of a random effect model (in order to cope with the presumptive heterogeneity in study design). I^2 statistic was then calculated to quantify the amount of inconsistency between included studies; it estimates the percentage of total variation across studies that is due to heterogeneity rather than chance. I^2 values ranging from 0 to 25% were considered to represent low heterogeneity, from 26% to 50% as moderate heterogeneity and above 50% as substantial heterogeneity. To investigate publication bias, funnel plots were initially generated: publication bias was evaluated by testing the null hypothesis that publication bias does not exist by means of the regression test for funnel plot asymmetry. The null hypothesis was rejected if the p-value is less than 0.10.

All calculations were performed in R (version 3.6.1; R Core Team, 2017. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/) and RStudio (version 1.2.5019) software by means of *meta* package (version 4.9-9), functions *metaprop* for pooling of HD prevalence. The meta package is an open-source add-on for conducting meta-analyses.

Results

Initially, 127 entries were identified, including a total of 41 abstracts from PubMed, and 86 from EMBASE and 22 Regional reports: as 43 of them were duplicated across the sources, 84 entries were initially screened. After applying the inclusion and exclusion criteria (Figure 1), and retrieving 2 further papers through the references of the research initially included in the analyses, a total of articles were included in the analyses and summarized, including 12 studies on seroprevalence, with a total of all of them summarized in Table 1 (13,14,24,15,17–23), and 6 case reports/series (12,24–28) (Table 2).

Seroprevalence studies – All but one study, that was performed by means of ELISA, were based on the immunoflorescence assay (IFA) (22), were performed between 1981 and 2019, and included either surveys on healthy subjects, or subjects affected by renal disorders, either Acute Renal Failure (ARF) or Chronic Renal Failure (CRF) (14,15,17,23,24). In turn, studies on healthy subjects reported on three distinctive populations: a) agricultural and forestry workers, and Soldiers or Veterans; b) urban population "at high risk" for interaction with rodents and hosts of Hantaviruses (i.e. mammologists, trappers, oarsmen, garbage collectors, river police, trappers and oarsmen, but also subjects with a previous diagnosis of chronic renal failure); c) reference general population from urban areas (13,14,29,15,17–22,24). A significant share of retrieved reports on seroprevalence exhibited with a certain overlapping of sampled subjects, that were largely drawn from three areas in various time points: Tuscany region (14,15,17,24), Cadore (a historical region in the Italian region of Veneto, in the mountainous northernmost part of the province of Belluno bordering on Austria, the Trentino-Alto Adige/Südtirol and Friuli-Venezia Giulia) (13,18–20), Rome and Tiber river valley (13,18–20), the Trentino Alto-Adige (21,22,29),

Eventually, the final sample included a total population of 5,336 subjects, i.e. 4,691 healthy subjects, and 645 subjects affected by ARF/CRF, with a total of 200 positive cases (3.7%). As shown in Table 1, the highest prevalence rates were identified in participants with underlying renal disorders, including either ARF, with or without previous exposure to rodents (i.e. 22.5% to 33.3%) (14,15,17,24), while subjects affected by CRF exhibited prevalence rates ranging from 2.3 to 7.3%. Among healthy subjects, higher shares of seropositivity for hantaviruses were identified in Veterans (20.0%, 95%CI 9.1% to 35.6%) (18), foresters from Cadore (i.e. 6.0% to 10.8%) (13,19,20), and Trentino. In this case, the reported prevalence increased from 0.2% in 2006 to 10.2% in 2018 (21,29).

Unfortunately, only 7 out of 12 studies included some insights about the viral agents (15,17,18,21,23,24,29), for a total of 99 diagnoses, with inconsistent reporting

Table 1. Summary of retrieved studies on Hantavirus serology in Italy. All studies, but the one from Kreidl et al. (22) (ELISA), were performed by means of immunofluorescence assay (IFA). Notes: PUUV = Puumala virus; DOBV = Dobrava Belgrade virus; ARF = acute renal failure; CRF = chronic renal failure.

Study	Timeframe (Years)	Geographical settings	Settings	No. of samples	Positive Samples (No., %)	Note
Lombardi et al. (17)	1981 – 1984	Tuscany region	*ARF of unknown origin*	54	17, 31.5%	PUUV = 9 (50.0%), Hantaan = 4 (22.2%), PUUV + Hantaan = 14 (77.8%)
			CRF in general population	44	1, 2.3%	
Leoncini et al. (15)	1985 – 1986	Tuscany region	*ARF after exposure to rodents (any)*	33	11, 33.3%	All cases negative for PUUV and DOBV
Salvadori et al. (24)	1989	Tuscany region	*Acute Renal Failure*	40	9, 22.5%	PUUV = 9 (100%)
			CRF in general population	22	1, 4.5%	
Lombardi et al. (14)	1989	Tuscany region	*ARF after exposure to rodents (any)*	63	19, 30.2%	-
			CRF in general population	22	1, 4.5%	-
Nuti et al. (18)	1990	Balkans (Nationwide)	*Ex-soldiers (exposed 1939 to 1945)*	40	8, 20.0%	PUUV = 2 (25.0%), DOBV = 5 (62.5%), Hantaan = 5 (62.5%), other = 2, (25.0%)
Nuti et al. (13)	1985 – 1990	Cadore[1]	*Foresters*	65	7, 10.7%	-
			Farmers	192	9, 4.7%	
		Rome	*Mammologists*	20	2, 10.0%	
			CRF in general population	51	3, 5.9%	
			Trappers	66	0, -	
			Oarsmen	58	0, -	
			Garbage collectors	21	0, -	
			River police	13	0, -	
		Nationwide	*General population*	1583	37, 2.3%	
Nuti et al. (19)	1987 – 1991	Cadore[1]	*General population*	350	8, 2.3%	
			Foresters	265	19, 7.1%	-
			Rangers	82	4, 4.8%	
			Farmers	395	17, 4.3%	
			Hunters	75	3, 4.0%	
			Soldiers	299	2, 0.7%	
			Fishermen	30	0, -	

(*Continued*)

Study	**Timeframe** (Years)	**Geographical settings**	**Settings**	**No. of samples**	**Positive Samples** (No., %)	**Note**
Nuti et al. (20)	1991	Cadore[1]	*Foresters*	250	22, 8.8%	-
			Rangers	52	2, 5.7%	
			Farmers	192	9, 4.7%	
			Hunters	60	2, 3.3%	
			Fishermen	30	0, -	
		Rome	*Mammologists*	20	2, 10.0%	
			CRF in general population	51	3, 5.9%	
			Trappers	66	0, -	
			Garbage collectors	21	0, -	
			Firemen	260	0, -	
			River police	13	0, -	
Kallio-Kokko et al. (21)	2000 – 2003	Autonomous Province of Trento	*Foresters*	488	1, 0.2%	DOBV = 1 (100%)
Kreidl et al. (22)	2004	Autonomous Province of Bolzano	*General population*	696	2, 0.3%	-
Tagliapietra et al. (29)	2015	Autonomous Province of Trento	*Foresters*	187	19, 10.2%	PUUV = 10 (52.6%), DOBV = 9 (47.4%)
			General population	113	5, 4.4%	PUUV = 1 (20.0%%), DOBV = 4 (80.0%)
Faolotto et al. (23)	2019	Piedmont	*IRC in general population*	371	27, 7.3%	Either PUUV or -DOBV

Cadore is a historical region in the Italian region of Veneto, in the northernmost part of the province of Belluno bordering on Austria, the Trentino-Alto Adige/Südtirol and Friuli-Venezia Giulia.

Table 2. Summary of case reports on Hantavirus in Italy. Notes: * = reports from Rovida et al. (25,26) deal with a shared case, but were included in the summary as the information reported were complimentary. HCPS = Hantavirus Cardiopulmonary Syndrome; HFRS = Hemorrhagic Fever with Renal Syndrome; PUUV = Puumala virus; N.A. = not available.

Study	Timeframe	Geographical settings	Age of case	Sex	Country of origin	Settings	Clinical presentation	Pathogen
Salvadori et al. (24)	1982	Tuscany region	N.A.	M	Italy	Working abroad (Siberia)	HFRS	Unspecified
Nuti et al. (12)	1987	Friuli-Venezia-Giulia	52	M	Italy	Resident at border with Yugoslavia (nowadays Slovenia)	HFRS	FOJNICA (?)
	1984	Friuli-Venezia-Giulia	N.A.	M	Italy	Resident at border with Yugoslavia (nowadays Slovenia)	HFRS	FOJNICA (?)
Caramello et al. (27)	2002	Turin	N.A.	M	Romania	Tourist (Romania)	HFRS	PUUV
Rovida et al. (25)*	2010	Pavia	59	M	Italy	Tourists (Cuba)	HCPS	New World Hantavirus
			28	M	Italy		HCPS	
			29	F	Italy		HCPS	
Rovida et al. (26)*	2010	Pavia	59	M	Italy	Tourist (Cuba)	HCPS	Sin Nombre
Valente et al. (28)	2016	Autonomous Province of Trento	16	F	Germany	Tourist (Autonomous Province of Trento)	HFRS	Unspecified

on the cross-positivity status. More precisely, Faolotto et al. did not report about the actual prevalence of PUUV and DOBV infections among the 27 positive cases they identified (23). As shown in Table 3, among the remaining 72 subjects, half of diagnoses were associated with PUUV (No. 36, 50.0%), while a total of 24 cases were positive for DOBV either a single diagnosis (No. 17, 23.6%) or associated with "*Hantaan*" virus (No. 7, 13.5%). Interestingly, no significant differences were reported between subjects with a farmer or a forestry background (No. 20), and other groups (No. 52), as in both cases PUUV represented the 50.0% of all diagnoses.

Pooled estimates for hantavirus prevalence were separately calculated in a random-effect model for healthy subjects and for cases with underlying renal disorders, and are reported in Figure 2,3 and 4. Briefly, the higher estimates were reported in associated with subjects with ARF (28.7%; 95%CI 22.1% to 36.2%) and CRF (6.6%, 95%CI 4.7% to 9.1%) (Figure 2), while the estimate for the general population (Figure 3) was 1.7% (95%CI 0.4 to 4.0), compared to 2.3% (1.0% to 5.0%) in cases of occupational exposure (Figure 4). In the latter case, estimates ranged from 0.0% (0.0 – 52.0%) in "high-risk" urban workers, to 3.8% (0.9% to 15.3%) in forestry workers, 4.0% (1.3-11.7%) in hunters, 4.9% (1.8-12.3%) in rangers, 5.3% in farmers (3.5%-8.0%). Interestingly, the seroprevalence in the military ranged between 0.7% (0.2% to 2.6%) in active soldiers from Cadore to 20.0% (10.3% to 35.2%) in veterans who had served in the Balkans during World War 2.

Heterogeneity for studies on healthy subjects was substantial (I^2 85%, $p < 0.001$ for studies on ARF/CRF, I^2 88%, $p < 0.001$ for studies on occupational groups, and I^2 83%, $p < 0.001$ for studies in the general population). On the contrary, subgroups of renal disorders were seemingly homogenous, with reported I^2 within subgroups equals to 0% both in ARF and CRF.

Focusing on the risk of receiving a serodiagnosis for any Hantavirus among the various population groups when compared with estimates from the general population (Figure 5), a stronger association was found in subjects affected by ARF (Odds Ratio 21.843, 95% Confidence Interval 13.703 to 34.029), followed by cases of CRF (OR 18.121, 95%CI 12.554 to 26.234), and Veteran soldiers (OR 13.591, 95%CI 6.261 to 31.360). Among rural exposure groups, an increased occurrence of seropositivity was identified among farmers (OR 3.053, 95%CI 1.787 to 5.103), rangers (OR 2.788, 95%CI 1.047 to 7.488), and eventually the whole of forestry workers (i.e. foresters, hunters and fishermen; OR 2.353, 95%CI 1.519 to 3.599).

The presence of publication bias was evaluated using funnel plots and regression test for funnel plot asymmetry, separately for studies performed on healthy subjects and affected by ARF/CRF. Each point in funnel plots represents a separate study and asymmetrical distribution indicates the presence of

Table 3. Seroprevalence for Hantaviruses detected among assessed studies broken down by participants with and without a forestry background. As Dobravirus (DOBV) was eventually identified only in 1992, with commercial kits for more uncommon Hantaviruses made available only in the following decade, earlier studies either identified a positivity towards "Hantaan virus" (i.e. an unknown Hantavirus similar to the prototype pathogen Hantaan virus) or "Hantavirus neither Puumala virus (PUUV) or Hantaan virus".

Pathogen	**Farmers / Forestry** (No., %)	**Other groups** (No., %)	**TOTAL** (No., %)
PUUV	10, 50.0%	26, 50.0%	36, 50.0%
PUUV only	10, 50.0%	10, 19.2%	20, 27.8%
+ Hantaan	0, -	16, 30.8%	16, 22.2%
+ DOBV	0, -	0, -	0, -
ALL OTHER	10, 50.0%	26, 50.0%	36, 50.0%
DOBV only	10, 50.0%	7, 13.5%	17, 23.6%
Hantaan only	0, -	4, 7.7%	4, 5.6%
Hantaan + DOBV	0,	7, 13.5%	7, 9.7%
TOTAL	20, 100%	52, 100%	72, 100%

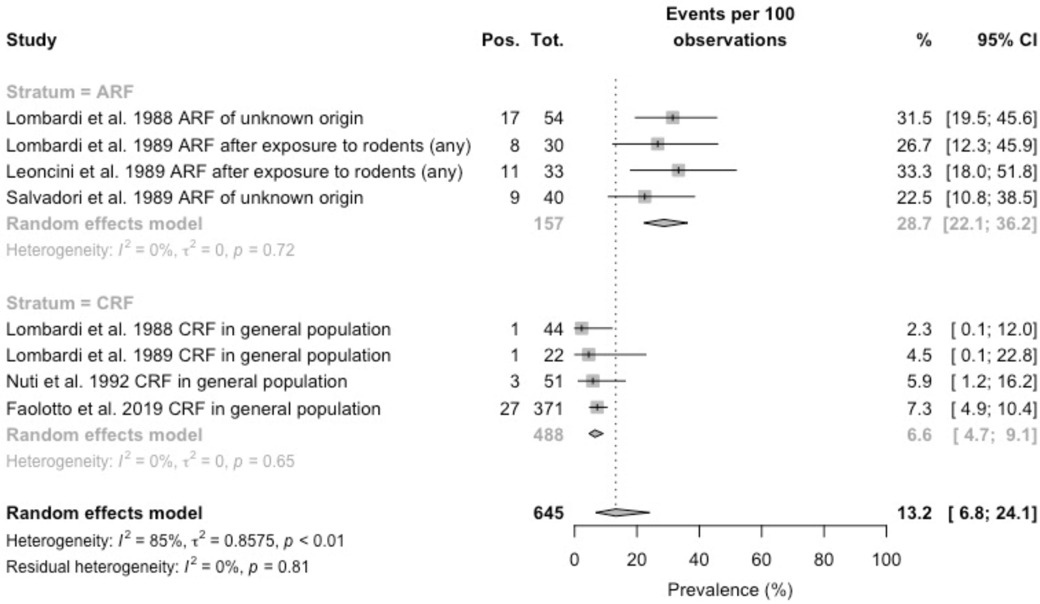


Figure 2. Forest plot of retrieved studies on the prevalence of Hantavirus infection in patients affected by Acute Renal Failure (ARF) and Chronic Renal Failure (CRF). As the studies from the group of Lombardi et al. and Leoncini et al. (14,15,17) reported on the very same populations in various time points, in the analyses each report excluded the data from the previous one. Estimated prevalence values were calculated by means of a random effect model; values are reported as % with correspondent 95% Confidence Intervals (95%CI).

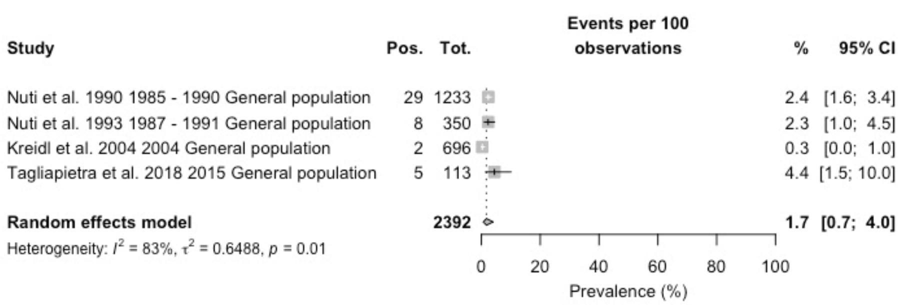


Figure 3. Forest plot of retrieved studies on the prevalence of Hantavirus infection in healthy subjects in the Italian general population. As the studies from Nuti et al. (13,19) reported on the very same populations in various time points, in the analyses each report excluded the data from the previous one. Estimated prevalence values were calculated by means of a random effect model; values are reported as % with correspondent 95% Confidence Intervals (95%CI).

publication bias. First, studies' effect sizes were plotted against their standard errors and the visual evaluation of the funnel plot suggested a significant publication (Figure 6 a/b). Still, such subjective evidence from the funnel plot was rejected after the regression test. Despite the apparent asymmetry of both graphs at the visual inspection, linear regression eventually rejected such hypothesis (t = -1.344, df = 21, p-value = 0.1933, and t = 0.014941, df = 6, p-value = 0.9886 for studies on healthy subjects and on subjects affected by renal disorders, respectively).

Case report studies. A total of 6 publications for 8 cases of Hantavirus infection were retrieved. Interestingly, the case detailed by Rovida et al. (26) was

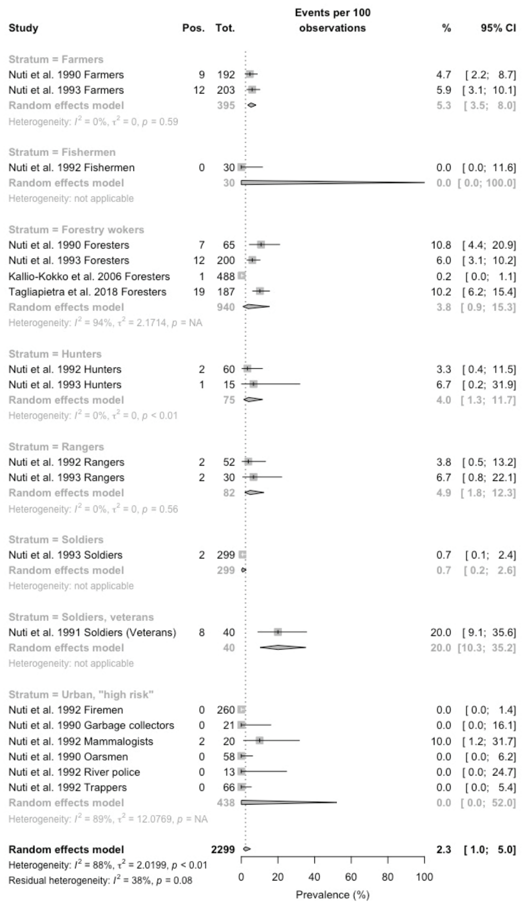


Figure 4. Forest plot of retrieved studies on the prevalence of Hantavirus infection in healthy subjects in Italy, broken down by occupational settings in rural/alpine settings, and urban areas (dichotomized as high risk of interaction with rodents vs. low risk). As the studies from Nuti et al. (13,18–20) reported on the very same populations in various time points, in the analyses each report excluded the data from the previous one. Estimated prevalence values were calculated by means of a random effect model; values are reported as % with correspondent 95% Confidence Intervals (95%CI).

originally reported by the very same authors in a small case series (25), representing a duplication. However, as the two publications complemented each one in various details, both documents were analyzed and summarized in Table 2. The majority of reported cases were of male sex (7/8, 87.5%), and occurred in subjects who had presumptively contracted the hantavirus infection abroad, either as tourists (25–28) or transfer workers. In two cases (27,28), as dealing with subjects with a foreign background, Authors were unable to assess

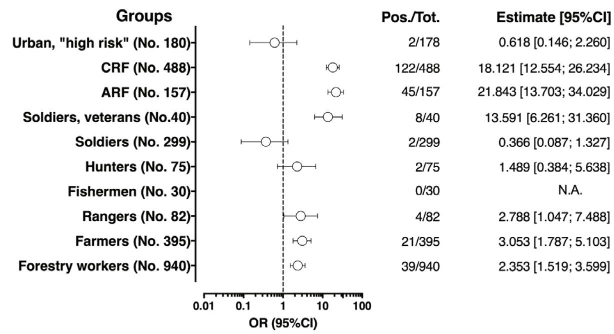
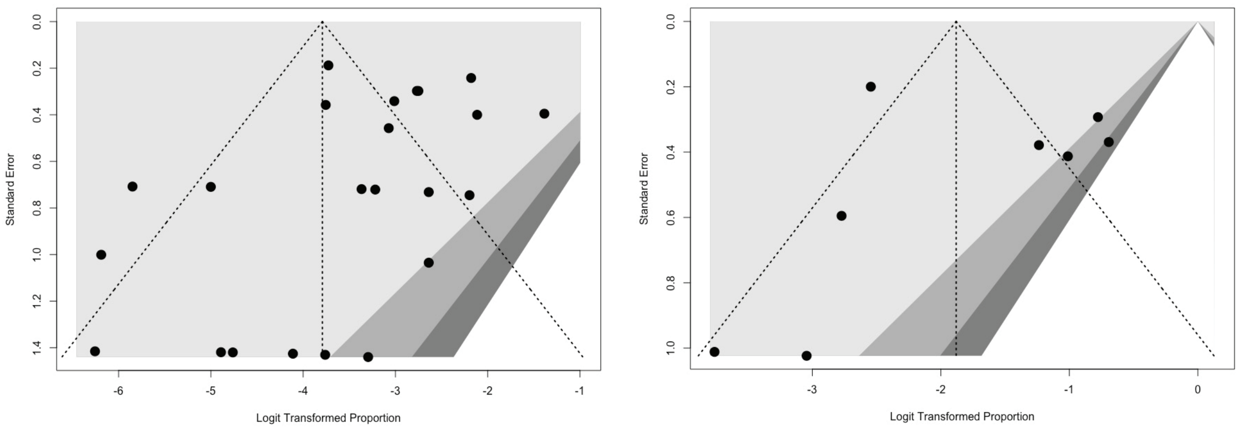


Figure 5. Association of positive status towards hantavirus seropositivity by population groups, assuming general population as the reference category (pooled: 44/2436; 1.7%, 95%CI 0.4 – 4.0). Note: N.A. not applicable.

whether the infection occurred in Italy or abroad. Similarly, in 2 cases occurring in residents in the Italian border region of Friuli Venezia Giulia, Authors were unable to ascertain whether the infection (suspected for Fojnica virus, but not confirmed) occurred in Italy or in the territory of the nearby Former-Yugoslavia republic of Slovenia (12). Interestingly, while 5 cases had a clinical presentation of HFRS, 3 cases occurred as HCPS suggesting the diagnosis of a New World Hantavirus, that was subsequently confirmed as an infection from Sin Nombre virus (26).

Discussion

During the last decades, Hantavirus have emerged as endemic and often ignored pathogens in all of Western Europe (9,30–34). Our meta-analysis on Hantavirus in Italy estimated a pooled seroprevalence of 1.7% for the general population (1981 – 2019). Such figures are substantially comparable with available seroprevalence data from Western Europe, with estimates ranging from less than 1% in Switzerland, 1.7% in Slovenia, to 1-2% in Austria, 1-3% in Germany, and even 4% in Greece (11,34–36). Even the significant heterogeneity of the seroprevalence in the retrieved studies, ranging from 0.3% to 4.4%, is consistent with available evidence, and was presumptively associated with the variable endemicity of hantavirus infection in the natural rodent hosts (20,21). Interestingly, the ecology of Hantaviruses in rodent



a) Studies on healthy subjects **b) Studies on subjects affected by renal disorders**

Figure 6. Contour-enhanced funnel plots of available studies on the Italian prevalence of Hantavirus infections, broken down as researches performed on healthy subjects and in studies on subjected affected by renal disorders, either chronic or acute renal failure. Despite the apparent asymmetry of both graphs at the visual inspection, it was ultimately rejected at linear regression (t = -1.344, df = 21, p-value = 0.1933, and t = 0.014941, df = 6, p-value = 0.9886 for studies on healthy subjects and on subjects affected by renal disorders, respectively).

hosts is highly variable, not only and more intuitively at geographical level, but also over time, following the complicated interaction between rodent hosts and their environment (1,37,38). For example, in 1995 German seroprevalence estimates ranged between 1 and 2%, but in 2005 actual figures climbed to 7% in the epidemic areas of Baden Württemberg and Lower Bavaria (31,39,40). On the other hand, the official figures from ECDC suggest that epidemic curve may have been somewhat slowed down only since the outbreak years of the early 2010s (33,41), with a seasonal pattern that is presumptively driven by food supplies. This provides ample food over winter that, associated with intrinsic effect of viral infection, eventually results in early reproduction and population irruption in the following year (1,33,37,38,41).

Consistently with previous reports from Western Europe (5,36,42–44), the risk of seropositivity was also significantly increased for certain occupational groups, particularly for those that favor human-rodent, including farmers (OR 3.053, 95%CI 1.787 to 5.103), rangers (OR 2.788, 95%CI 1.047, 7.488), and more generally speaking, the forestry workers as a whole (OR 2.343, 95%CI 1.519 to 3.599). Compared to the healthy general population, also subjects with either acute or chronic renal disorders had an increased risk for being IgG seropositive towards Hantaviruses (OR 21.843 95%CI 13.703 to 34.029, and OR 18.121, 95%CI 12.554 to 26.234). As long-term studies on HFRS indicate that Hantavirus infection may be associated with chronic renal dysfunction, including reduced glomerular filtration rate, proteinuria, and hypertension (45), our data suggest that Hantaviruses could contribute to the burden of kidney disease in Italy (46–48).

In other words, while official figures state that no case of Hantavirus infection has occurred in Italy at least since 2012 (32,49), serological surveys suggest that such pathogens, still relatively rare, are actively circulating, and such evidence is in turn consistent with serological studies on rodents hosts (19–21). Moreover, we have collected a certain evidence that severe hantavirus infections have actually occurred in travelers and tourists, but also in cases in which an autochthonous origin could not been ruled out, there was apparently no official report to the National authorities, with a subsequent lack of reporting to the competent European Centre for Disease Prevention and Control (27,28).

In effects, and despite the absence of officially reported cases, it should be stressed that the actual non-occurrence of hantavirus infections would have been somewhat surprising, for several reasons. Firstly, Italy shares its border with countries that are not only endemic for Hantaviruses such as PUUV and DOBV (i.e. Austria, Slovenia, France, Switzerland and Germany), but between 2005 and 2017 have also experienced a sustained outbreak of HFRS, with a cumulative occurrence of around 5,000 cases, mostly of them in the Alpine and sub-Alpine areas (4,8).

Second, studies on the ecology and phylogenetic characteristics of PUUV and DOBV collectively suggest that one of the original niches of both European Hantaviruses and their hosts (and particularly the bank vole, or *Myodes glareolus*) may be found in the Alpe Adria region (3,37,38), where some of the studies included in this meta-analysis have been performed, reporting very high seroprevalence rates, particularly among forestry workers (19,20).

Third, there is sound evidence that some species of Hantaviruses have been actively circulating in rodents in various areas of the Italian peninsula, with first human cases occurring at least since the beginning of '90s, if not earlier (13,20,21,50,51). In this regard, serological surveys both on humans and rodents suggest that PUUV infections, at least until recently, have been significantly more prevalent compared to other pathogens, and particularly DOBV. As up to 95% of PUUV infections remain subclinical, and even the symptomatic infections may easily be overlooked, due to lack of awareness among clinicians, the actual number of hantavirus infections may have been extensively underestimated of improperly diagnosed as a flu-like syndrome (1,3,52,53). Not coincidentally, among the eight case reports we identified, only one was associated with a PUUV infection (12,24–28), and also in the earlier reports on ARF/CRF patients of Leoncini et al (15) and Lombardi et al (15,17), PUUV accounted to a maximum of 50% of cases, while available reports otherwise suggest its absolute predominance (1,4), up to 97% of all cases (41). However, such explanation is only partially consistent with available data. Even though a proper serotyping was available in only 72 out of the 200 total cases we retrieved (15,17,18,21,23,24,29), and some of the studies were performed before commercially available kits for DOBV were made available, at least in the more recent reports on the general Italian population the latter was as much as prevalent as the PUUV cases (22,29).

Despite their potential interest, our data should be interpreted with some cautions. On the one hand, two of the four studies on the general population included in our metanalysis were performed in the mid '80s (13,19), another one was completed in the early 2000s (21), and only the recent study of Tagliapietra et al. (29) was accomplished after the decade 2005-2017, i.e. the outbreaks years for central Europe (21,34,35,52). As the seroprevalence estimates we retrieved were substantially analogous to the contemporary ones form nearby European countries, a parallel increase during outbreak years cannot be definitively ruled out. Therefore, we can speculate that our estimates largely underestimated current prevalence rates (3,9,29,33,52). Not coincidentally, the two studies from the Trentino Province were separated in time by around a decade, and the prevalence rates have literally skyrocketed, from the original 0.2% reported in foresters in 2006 to the 10.2% of 2018 (21,29). In this regard, it should be stressed that such studies have been extensively performed before the ongoing Italian migrant crisis (54,55), and that Alpe Adria and Trentino Region are characterized by a seasonal workforce that is mainly drawn from the Balkan regions (55–57): as living in precarious, non-hygienic settings, and occupational exposures represent the most significant risk factor for hantavirus infection (4,30,43,58), we could speculate that such population groups may be characterized by even higher occurrence of Hantavirus infections.

On the other hand, most of the evidence we reported was drawn from specific geographical areas, including the mountainous region of Trentino-Südtirol, the Alpe Adria region of Cadore, the area of Florence in Tuscany Region, and the urban area of Rome. While some of the studies have deliberately included occupational groups that were at a presumptively higher risk for Hantavirus infections (i.e. forestry workers, farmers, but also mammologists), the inclusion/exclusion strategy of studies on the general population and reporting about cases of idiopathic ARF/CRF were often unclear (12,13,19–21,29). In other words, we cannot rule out that also the studies namely reporting on "*general population*" actually included subjects that, because of non-occupational exposures (e.g.

hobby farmers, but also backpackers, etc.), had a still significant (and often increased) but not reported risk to be exposed to microbial pathogens such as the hantaviruses (59–61), not truly representing a snapshot of the general Italian population.

Moreover, the comparison of seroprevalence rates across various studies and different decades is not only intrinsically complicated, but the resulting figures may be either over- or underestimated because of various methodologies of laboratory assessment. For example, an earlier study on blood donors from St. Gallen Switzerland found a prevalence of 3.8% at median fluorescence intensity, that dropped to 0.6% in IFA, while a subsequent seroprevalence study on 4,559 Swiss blood donors and 1,810 military personnel identified an ELISA-based prevalence of 9.4%, that in turn dropped to 0.3 to 0.5% in immunofluorescence and/or immunoblot assays (11,36). In this regard, nearly all reports were based on the highly reliable IFA assays, allowing us to substantially rule out a possible overestimation due to the diagnostic tests. Similarly, most of comparable studies from Western Europe received a confirmatory IFA test, allowing an easier comparison between the different reports (10,37,39,40,62).

Conclusions

Hantavirus infections in Italy are neither novel nor uncommon, but are mostly unnoticed. In fact, while seroprevalence studies collectively confirm that human infections do occur, at least in certain areas characterized by the likely interaction between humans and rodents, the characteristics of case-control studies seemly suggest a possible reporting bias. In other words, as the large majority of human cases is reasonably associated with mild, indolent clinical features, most of them may occur substantially unnoticed to any medical professionals. Moreover, the low suspicion index usually deserved to a disease otherwise understood as uncommon, rare or somewhat "*exotic*" may have in turn impaired a proper diagnosis even in most of symptomatic cases. Not coincidentally, the majority of case reports and case series we were able to retrieve either involved particularly severe clinical features or were associated with very uncommon features and/or pathogens (i.e. New World Hantaviruses, or Hantaviruses from the Balkans). In summary, we think that an up-to-date assessment of Hantavirus seroprevalence both in the reservoir host species and in the general population, specifically targeting some selected population groups (i.e. agricultural and forestry workers; migrants/refugees, etc.) is needed. At the same time, an appropriate inquiry of ARF/CRF cases of unknown etiology may be useful in order to allow an early identification of potential outbreaks and spillover.

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