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/HFRS (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.
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).

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       | Cadore¹               | Foresters                                   | 65             | 7, 10.7%                                                       |                                                                     |
|                      |                   |                      | Farmers                                     | 192            | 9, 4.7%                                                        |                                                                     |
|                      | Rome              | Mammalogists          |                                              | 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       | Cadore¹               | 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                          | 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), hunters (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).

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.

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 Hantavirus in rodent...
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 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).

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 metaanalysis 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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References

1. Avsić-Županc T, Saksida A, Korva M. Hantavirus infections. Clin. Microbiol. Infect. 2019;21:e6–16. DOI 10.1111/1469-0691.12291
2. Liu R, Ma H, Shu J, et al. Vaccines and Therapeutics Against Hantaviruses. Front. Microbiol. 2020;10:2989. DOI 10.3389/fmicb.2019.02989
3. Castel G, Chevenet F, Razzaoui M, et al. Phylogeography of puumala orthohantavirus in Europe. Viruses 2019;11(8):679. DOI 10.3390/v11080679
4. Heyman P, Vaheri A, Lundkvist Å, Avsic-Zupanc T. Hantavirus infections in Europe: from virus carriers to a major public-health problem. Expert Rev. Vaccines 2009;7(2):205–17.
5. Schöffel N, Braun M, Bendels MHK, Brüggmann D, Groneberg DA. Die humane Hantavirus-Infektion: Eine Literaturübersicht. Zentralblatt fur Arbeitsmedizin, Arbeitsschutz und Ergon. 2018;68(2):94–17. DOI 10.1007/s40664-017-0223-2
6. Laenen L, Vergote V, Calisher CH, et al. Hantaviridae: Current classification and future perspectives. Viruses 2019;11(9):788. DOI 10.3390/v11090788
14. Lombardi M, Salvadori M, Ciciani AM, et al. Nefropatia da Hantavirus. Proceeding 51st Natl. Congr. Ital. Soc. Nephrol. - Milan, 12/15 October, 2016 (Internet) 2016;P254. Available from: http://www.provincia.bz.it/salute-benessere/salute/pubblicazioni.asp?publ_page=3#download-area-ids=34543

15. Leocinci F, Bartolozzi D, Buonamici C, et al. New etiological agents of nephropathy in Italy. The Hantavirus. G. Mal. Infett. Parasit. 1989;41(6):68–72.

16. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med. 2009;6(7):e1000097. DOI 10.3736/jcim2009018

17. Lombardi M, Salvadori M, Bandini S, et al. Nefropatia epidemica da Hantavirus. Proceeding 51st Natl. Congr. Ital. Soc. Occup. Med. Ind. Hyg. - Firenze, December 13-16, 1998;689–92.

18. Nuti M, Agostini M, Albini E, Avsic-Zupanc T, Kraigher A. Hantaan antibody in Italian ex-soldiers who served in the Balkans. Lancet 1991;338(8777):1277. DOI 10.1016/0140-6736(91)92147-T

19. Nuti M, Amaddeo D, Crovatto M, et al. Infections in an alpine environment: Antibodies to hantaviruses, leptospira, rickettsiae, and Borrelia burgdorferi in defined Italian populations. Am. J. Trop. Med. Hyg. 1993;48(1):20–5. DOI 10.4269/ajtmh.1993.48.20

20. Nuti M, Amadeo D, Autorino GL, et al. Seroprevalence of antibodies to hantaviruses and leptospirias in selected Italian population groups. Eur. J. Epidemiol. 1992;8(1):98–102. DOI 10.1007/BF00334979

21. Kallio-Kokko H, Laakkonen J, Rizzoli A, et al. Hantavirus and arenavirus antibody prevalence in rodents and humans in Trentino, Northern Italy. Epidemiol. Infect. 2006;134(4):830–6. DOI 10.1017/S0950568805005431

22. Kreidl P, Walder G, Morosetti G. Studio TIMO - Sieroprevalenza di varie malattie trasmissibili attraverso zecche, zanzare e roditori nel Tirol Settentrionale, Orientale e Alto Adige (Internet). Oss. Epidemiol. della Prov. Auton. di Bolzano, Auton. Prov. Bolzano, Italy - Med. Univ. Innsbruck, Innsbruck Austria. Bolzano / Innsbruck; 2004. Available from: http://www.provincia.bz.it/salute-benessere/salute/pubblicazioni.asp?publ_page=3#download-area-ids=34543

23. Faolotto G, Korhonen EM, Minisini R, et al. Presenza di sieropositività anticorpale per Hantavirus e Arenavirus in pazienti del Piedmont Nordorientale. Proc. 48th Natl. Congr. AMCLI - Rimini, Novemb. 9th - 12th 2019 (Internet) 2019;P246. Available from: http://www.amcili.it/eventi/congressi-nazionali/

24. Salvadoni M, Lombardi M, Nicoletti L. Acute renal involvement in Hantavirus infection: First report in Italy. J Nephrol 1989;1:17–22.

25. Rovida F, Percivalle E, Sarasini A, Chichino G, Baldanti F. P1000 - Imported symptomatic Hantavirus infection in three family members travelling from Cuba. 21st ECCMID / 27th ICC - 07 May 2011 - 10 May 2011 Milan; 2011. p. P1000.

26. Rovida F, Percivalle E, Sarasini A, Chichino G, Baldanti F. Imported hantavirus cardiopulmonary syndrome in an Italian traveller returning from Cuba. New Microbiol. 2013;36(1):103–5.

27. Caramello P, Canta F, Bonino L, et al. Puumula virus pulmonary syndrome in a Romanian immigrant. J. Travel Med. 2002;9(6):326–9. DOI 10.1183/13222514.2002.9.6.326

28. Valente F, Zarantonello D, De Gaetano A, Gentili A, Veniero P, Brunori G. Nefropatia da Hantavirus: una diagnosi da considerare. Proc. 57th Annu. Congr. Ital. Soc. Nephrol. - Milan, 12/15 October, 2016 (Internet) 2016;P254. Available from: http://www.provincia.bz.it/salute-benessere/salute/pubblicazioni.asp?publ_page=3#download-area-ids=34543

29. Tagliapietra V, Rosà R, Rossi C, et al. Emerging Rodent-Borne Viral Zoonoses in Trento, Italy. Ecohealth 2018;15(3):695–704. DOI 10.1007/s10393-018-1335-4

30. Ahlm C, Thelin A, Elgh F, et al. Prevalence of antibodies specific to Puumula virus among farmers in Sweden. Scand. J. Work. Environ. Heal. 1998;24(2):104–8. DOI 10.5271/sjweh.286

31. Kimmig P, Silva-González R, Backe H, et al. Epidemiologie von hantaviren in Baden-Württemberg. Gesundheitswesen 2001;63(2):107–12. DOI 10.1055/s-2001-10961
32. European Centre for Disease Prevention and Control (ECDC). Annual Epidemiological Report for 2016 - Hantavirus infection (Internet). Annu. Epidemiol. Rep. 2016. Stockholm; 2018. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/AER_for_2016-mumps-rev.pdf

33. Binder F, Drewes S, Inholt C, et al. Heterogeneous Puumala orthohantavirus situation in endemic regions in Germany in summer 2019. Transbound. Emerg. Dis. 2020;67(2):502–9. DOI 10.1111/tbed.13408

34. Vapalahti O, Mustonen J, Lundkvist Å, Henttonen H, Pylusnin A, Vahteri A. Hantavirus infections in Europe. Lancet Infect. Dis. 2003;3(10):653–61. DOI 10.1016/S1473-3099(03)00774-6

35. Jonsson CB, Figueiredo LTM, Vapalahti O. A global perspective on hantavirus ecology, epidemiology, and disease. Clin. Microbiol. Rev. 2010;23(2):412–41. DOI 10.1128/CMR.00062-09

36. Schultze D, Fierz W, Matter HC, Bankoul S, Niedrig M, Schmiedl A. Cross-sectional survey on hantavirus serorelevance in Canton St. Gallen, Switzerland. Swiss Med. Wkly. 2007;137(1–2):21–6. DOI 2007/01/smw-11594

37. Olsson GE, Leirs H, Henttonen H. Hantaviruses and their hosts in Europe: Reservoirs here and there, but not everywhere? Vector-Borne Zoonotic Dis. 2010;10(6):549–61. DOI 10.1089/vbz.2009.0138

38. Milholland MT, Castro-Arellano I, Garcia-Peña GE, Mills JN. The ecology and phylogeny of hosts drive the enzootic infection cycles of hantaviruses. Viruses 2019;11(7):1–14. DOI 10.3390/v11070671

39. Mertens M, Hofmann J, Pettraityte-Burneikiene R, et al. Seroprevalence study in forestry workers of a non-endemic region in eastern Germany reveals infections by Tula and Dobrava-Belgrade hantaviruses. Med. Microbiol. Immunol. 2011;200(4):263–8. DOI 10.1007/s00430-011-0203-4

40. Zöller L, Faulde M, Meisel H, et al. Seroprevalence of hantavirus antibodies in Germany as determined by a new recombinant enzyme immunoassay. Eur. J. Clin. Microbiol. Infect. Dis. 1995;14(4):305–13. DOI 10.1007/BF02116523

41. European Centre for Diseases Prevention and Control (ECDC). Hantavirus Infection. Stockholm; 2017.

42. Antoniadis A, Le Duc JW, Daniel-Alexiou S. Clinical and epidemiological aspects of hemorrhagic fever with renal syndrome (HFRS) in Greece. Eur. J. Epidemiol. 1987;3(3):295–301. DOI 10.1007/BF00149739

43. Covert DJ, Langley RL. Infectious disease occurrence in forestry workers: A systematic review. J. Agromedicine 2002;8(2):95–111. DOI 10.1300/J096v08n02_12

44. Moll van Charante AW, Groen J, Osterhaus ADME. Risk of infections transmitted by arthropods and rodents in forestry workers. Eur. J. Epidemiol. 1994;10(3):349–51. DOI 10.1007/BF0179362

45. Pergam SA, Schmidt DW, Nofchissey RA, Hunt WC, Harford AH, Goade DE. Potential Renal Sequelae in Survivors of Hantavirus Cardiopulmonary Syndrome. Am J Trop Med Hyg (Internet) 2009;80(2):279–95. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3624763/pdf/nihms412728.pdf

46. Jayasumana C. Chronic Interstitial Nephritis in Agricultural Communities (CINAC) in Sri Lanka. Semin. Nephrol. Elsevier Inc.; 2019;39(3):278–83. DOI 10.1016/j.sneph.2019.02.006

47. Adams K, Jameson L, Meigh R, Brooks T. Hantavirus: An infectious cause of acute kidney injury in the UK. BMJ Case Rep. 2014;10–2. DOI 10.1136/bcr-2014-205529

48. Engdahl TB, Crowe JE. Humoral Immunity to Hantavirus Infection. mSphere 2020;5(4):e00482-20. DOI 10.1128/msphere.00482-20

49. European Centre for Diseases Prevention and Control (ECDC). Annual Epidemiological Report for 2015 - Hantavirus Infection. Stockholm; 2017.

50. Mansueto S, Peters CJ, Tringham G, et al. Prime ricerche sulla presenza di anticiropi anti-virus Hantaan in Sicilia Occidentale. G Mal Infet Parasitt 1987;39:99–101.

51. Mansueto S, Rini GB, Vitale G, et al. Febbre emorragica con sindrome renale e ratti di allevamento. Ricerca di anticiropi anti-virus Hantaan in un stabulario. G Mal Infet Parasitt 1987;39:102–3.

52. Makary P, Kanerva M, Ollgren J, Virtanen MJ, Vapalahti O, Lyytikäinen O. Disease burden of Puumala virus infections, 1995–2008. Epidemiol. Infect. 2010;138(10):1484–92. DOI 10.1017/S0950268810000887

53. Bi Z, Formenty PBM, Roth CE. Hantavirus infection: a review and global update. J. Infect. Dev. Ctries. 2008;2(1):3–23. DOI 10.3855/jidc.317

54. Odone A, Riccò M, Morandi M, Borrini BM, Pasquarella C, Signorelli C. Epidemiology of tuberculosis in a low-incidence Italian region with high immigration rates: Differences between not Italy-born and Italy-born TB cases. BMC Public Health (Internet) 2011;11:376. Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-79956228648&partnerID=MN8TOARS

55. Riccò M, Garbarino S, Bragazzi NL. Migrant Workers from the Eastern-Mediterranean Region and Occupational Injuries: A Retrospective Database-Based Analysis from North-Eastern Italy. Int J. Occup. Environ. Med. 2019;16:673. DOI 10.3390/ijomh16040673

56. Riccò M. Air temperature exposure and agricultural occupational injuries in the autonomous province of Trento (2000–2013, north-eastern Italy). Int. J. Occup. Environ. Health 2018;31(3). DOI 10.13075/ijomeh.1896.01114

57. Riccò M, Vezzoli L, Balzarini F, Odone A, Signorelli C. Air temperatures and occupational injuries in the autonomous province of Trento (2000–2013, north-eastern Italy). Int. J. Occup. Environ. Health 2018;31(3). DOI 10.13075/ijomeh.1896.01114

58. Wang X, Shen W, Qin Y, et al. Prime ricerche sulla presenza di anticiropi anti-virus Hantaan in Sicilia Occidentale. G Mal Infet Parasitt 1987;39:99–101.

59. Riccò M, Razio B, Panato C, Poletti L, Signorelli C. Knowledge, Attitudes and Practices of Agricultural Industries: a report from Northern Italy (2000–2013). Ind. Health 2018;31(3). DOI 10.13075/ijomeh.1896.01114
60. Riccò M, Vezzosi L, Mezzoiuso AG. Occupational Eye Injury in the agricultural settings: a retrospective study from North-Eastern Italy. Acta Biomed 2020;90(4):457–67.

61. Riccò M, Bragazzi NL, Vezzosi L, et al. Knowledge, Attitudes, and Practices on Tick-Borne Human Diseases and Tick-Borne Encephalitis Vaccine among Farmers from North-Eastern Italy (2017). J. Agromedicine Taylor & Francis; 2020;25(1):73–85. DOI 10.1080/1059924X.2019.1659204

62. Groen J, Gerding MN, Jordans JGM, Clement JP, Nieuwenhuijs JHM, Osterhaus ADME. Hantavirus infections in The Netherlands: Epidemiology and disease. Epidemiol. Infect. 1995;114(2):373–83. DOI 10.1017/S0950268800058003

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