

Epidemiology of Toscana Virus in Italy (2018-2020), a summary of available evidences

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To the Editor,

Toscana Virus (TosV) is an arthropod-borne negative-stranded RNA virus belonging to the order of *Bunyvirales*, family of *Phenuiviridae* (1,2). Originally isolated in 1971 in Tuscany, TosV is highly prevalent in countries bordering the northern shores of Mediterranean basin, mirroring the ecology of competent vectors (i.e. genera *Phlebotomus* and *Sergentomyia*) (1–6). For instance, available reports from Italian regions of Piemonte, Emilia Romagna, Tuscany, Umbria, Puglia, Sicily and Sardinia have reported a prevalence for specific IgG antibodies ranging from 1.0% to 41.9% among healthy residents, and even more higher in some occupational groups (e.g. agricultural and forestry workers) (3–6). While it is quite obvious that most of incident cases occur as pauci-symptomatic, the relatively high occurrence of IgM antibodies among patients complaining neurological symptoms (ranging between 4.7% to 27.2%) from the same areas suggests that a limited share of cases may develop a far more severe disorder (1,5).

Because of its potential epidemiological significance, since 2018 Italian National Health Service has included TosV neuroinvasive infections in the special surveillance for human arboviral infections, with periodic bulletins (<https://www.epicentro.iss.it/arbovirosi/bollettini>), whose content is subsequently summarized and discussed. Overall (Table 1), 182 cases of neuroinvasive TosV infections have been reported since 2018,

with a case fatality ratio of 0.05%. Crude Incidence Rate was estimated in 0.101 cases per 100,000 (95% Confidence Interval (95%CI) 0.087-0.117), with an age-adjusted Incidence Rate (AIR) equals to 0.100 per 100,000, 95%CI 0.001-0.212. AIR were also heterogeneous across the timeframe 2018-2020, being greater in 2018 (0.149 per 100,000), and then decreasing in the following years (0.093 and 0.060 for 2019 and 2020, respectively), while the majority of neuroinvasive TosV cases consistently occurred during the months of August (38.5%), July (28.0%), and September (20.3%).

Such a trend mirrored that of other arboviruses, and particularly West Nile Virus (WNV), that has been explained through the ecology of the vector (7,8). Similarly to mosquitoes, intense warmth followed by precipitation deficits stimulate the replication of Phlebotomine, whose circulation is therefore particularly intense between July and September (9). Unsurprisingly, 2018 was a record-breaking climate outlier in terms of summer temperatures, humidity, and lack of precipitation, that conversely were particularly intense during spring, and also Phlebotomine experienced an unprecedented thriving (1,9).

The role of the competent vector may also explain the increased risk for neuro-invasive TosV infections among males (70.3% of total cases) compared to females (Risk Ratio 2.498, 95%CI 1.817-3.434) (Table 2), as they are more commonly involved in outdoor activities (e.g. agriculture, forestry, and construction industries),

Table 1. Pooled data on incident cases of Toscana virus in Italy (2018 – 2020) according to official bulletins of the National Surveillance System for Arboviroses (data were retrieved from <https://www.epicentro.iss.it/arboviroosi/bollettini>).

	POOLED (No./182, %)	2020 (No./36, %)	2019 (No./56, %)	2018 (No./90, %)
Demographics				
Male	128, 70.3%	27, 77.8%	39, 69.6%	62, 68.9%
Age (years)				
0 to 39	70, 38.5%	13, 36.1%	21, 37.5%	36, 40.0%
40 to 59	66, 36.3%	14, 38.9%	16, 28.6%	36, 40.0%
60 or more	46, 25.3%	9, 25.0%	19, 33.9%	18, 20.0%
Regions				
<i>Emilia-Romagna</i>	111, 61.0%	28, 77.8%	33, 58.9%	50, 55.6%
<i>Tuscany</i>	35, 19.2%	3, 8.3%	14, 25.0%	18, 20.0%
<i>Marche</i>	23, 12.6%	2, 5.6%	3, 5.4%	18, 20.0%
<i>Lazio</i>	5, 2.7%	1, 2.8%	3, 5.4%	1, 1.1%
<i>Sicily</i>	5, 2.7%	2, 5.6%	3, 5.4%	0, -
<i>Piemonte</i>	2, 1.1%	0, -	0, -	1, 1.1%
<i>Abruzzo</i>	1, 0.5%	0, -	0, -	2, 2.2%
Month				
<i>January</i>	0, -	0, -	0, -	0, -
<i>February</i>	0, -	0, -	0, -	0, -
<i>March</i>	0, -	0, -	0, -	0, -
<i>April</i>	0, -	0, -	0, -	0, -
<i>May</i>	2, 1.1%	2, 5.6%	0, -	0, -
<i>June</i>	15, 8.2%	6, 16.7%	4, 7.1%	5, 5.6%
<i>July</i>	51, 28.0%	17, 47.2%	12, 21.4%	22, 24.4%
<i>August</i>	70, 38.5%	7, 19.4%	26, 46.4%	37, 41.1%
<i>September</i>	37, 20.3%	4, 11.1%	12, 21.4%	21, 23.3%
<i>October</i>	5, 2.7%	0, -	2, 3.6%	3, 3.3%
<i>November</i>	2, 1.1%	0, -	0, -	2, 2.2%
<i>December</i>	0, -	0, -	0, -	0, -
Deaths	1, 0.05%	0, -	0, -	1, 1.1%

particularly in the evening, at the peak of phlebotomine circulation (1,4). On the contrary, despite the majority of incident cases occurred among and in subjects aged 0 to 39 years (38.5%), age groups 40 to 59 years-old and ≥ 60 years-old scored a risk for developing neuro-invasive infection similar to that of younger subjects.

Even though earlier reports strongly associated TosV infections with the Tuscany region (1,5,6), 61.0% of neuroinvasive cases occurred in Emilia Romagna, with a crude incidence rate two times higher that

reported by other regions characterized by viral circulation, i.e. Tuscany and Marche (0.830 per 100,000, 95%CI 0.683-0.999 vs. 0.314, 95%CI 0.219-0.437, and 0.508, 95%CI 0.319-0.756, respectively). Again, such features may be explained through the interplay between climate and competent vector, as the Po River Valley where Emilia Romagna resides is particularly vulnerable to climate change(10).

In summary, official data on TosV neuro-invasive infections point towards a persistent, albeit not

Figure 2. Crude incidence rates and risk ratio for Toscana virus infections in Italy (2018-2020; cases per 100,000) by gender, age group, and region of occurrence. Note: 95%CI = 95% confidence intervals (data were retrieved from <https://www.epicentro.iss.it/arbovirosi/bollettini>).

	Risk Ratio (95%CI)	Incidence per 100,000 (95%CI)
Total	-	0.101 (0.087; 0.117)
Gender		
Male	2.498 (1.817; 3.434)	0.146 (0.122; 0.174)
Female	REF	0.058 (0.044; 0.076)
Age Group		
0 to 39	REF	0.097 (0.076; 0.123)
40 to 59	1.221 (0.873; 1.710)	0.119 (0.092; 0.151)
60 or more	0.896 (0.617; 1.299)	0.087 (0.064; 0.116)
Region		
<i>Emilia-Romagna</i>	REF	0.830 (0.683; 0.999)
<i>Tuscany</i>	0.379 (0.259; 0.554)	0.314 (0.219; 0.437)
<i>Marche</i>	0.607 (0.387; 0.951)	0.508 (0.319; 0.756)
<i>Lazio</i>	0.035 (0.014; 0.085)	0.029 (0.009; 0.067)
<i>Sicily</i>	0.041 (0.017; 0.100)	0.034 (0.011; 0.079)
<i>Piemonte</i>	0.019 (0.005; 0.075)	0.015 (0.002; 0.056)
<i>Abruzzo</i>	0.031 (0.004; 0.221)	0.026 (0.001; 0.143)

sustained, circulation of the pathogen. However, it should be stressed that neuro-invasive cases represent nothing more than the tip of the iceberg, or rather a proxy of the actual incident cases (1). Another significant limitation of our estimate is that TosV is often overlooked as a cause of neurological disorders, and most cases of aseptic meningoencephalitis may have been improperly assessed, with eventual underestimation of actual incidence rates (1–3). Therefore, medical professional must be aware that all cases of “summer influenza” (i.e. influenza-like illnesses occurring during the summer months, when the circulation of the influenza virus usually reaches its nadir in the Northern hemisphere) must be properly investigated, in order to both improve our understanding of the epidemiology of arboviruses including TosV, and guaranteeing the access of all patients to early and appropriate treatment.

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