

Epidemiological assessment of the first COVID-19 epidemic wave in Lombardy. A systematic review

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Abstract. *Background and aim:* After the first cases of COVID-19 detected in Wuhan (China), the virus rapidly spread in the world, so much so that on February 20 the first autochthonous case was officially identified in Italy. However, this person had no apparent history of travel abroad or contact with people tested positive for the virus. For this reason, the aim of this literature review was to reconstruct the epidemiological dynamics of the first wave of SARS-CoV-2 infection in the Lombardy Region. *Methods:* To this end, a systematic review was carried out on PubMed/MEDLINE and EMBASE, and on grey literature. All article assessing incidence, mortality and hospitalizations by Lombardy province and municipality, and the impact of the main containment and organizational measures were considered eligible. In addition, data on general mortality and mortality due to COVID-19, hospital admission, and serological and environmental were also retrieved. *Results:* From the included studies, it emerged that Lombardy was the first European region in which the virus began to circulate as early as January 2020 (and probably even earlier). Despite the high number of cases and deaths recorded, the reproduction number observed in Lombardy Region was, at the beginning of March 2020, the same (or lower) than in other regions. *Conclusions:* In conclusion, data of the first epidemic wave in Lombardy, compared to other Italian and foreign regions, highlight the extreme criticality of having had the first autochthonous case (and the first substantial outbreaks) when knowledge was still scarce and individual prevention measures were not widespread. (www.actabiomedica.it)

Key words: COVID-19, Lombardy, epidemiology, systematic review

Introduction

On 31 December 2019, the Wuhan Municipal Health Commission reported to the World Health Organization (WHO) a cluster of pneumonia of unknown aetiology detected in Wuhan City, Hubei Province of China (1). This new cluster of pneumonia had initially been identified as a new type of coronavirus, later detected as the “Severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2) (1). On February 11, the WHO established COVID-19 as

the name of the respiratory disease caused by the new coronavirus (2), and on March 11 the WHO declared the state of pandemic (2). In the meantime, the virus spread in the world rapidly (3), so much so that on February 20 2020, the first autochthonous case was officially identified in Italy (4). However, this person had no history of travel abroad or contact with people tested positive for the virus. For this reason, it was suspected, since the beginning, that the virus arrived in Italy earlier compare to the first official identified case. Based on these considerations, a systematic review of

both scientific papers and grey literature has been conducted in order to perform a retrospective epidemiological analysis useful to establish more precisely the real beginning of the epidemics in Italy.

The aim of this literature review was to reconstruct the epidemiological dynamics of the first wave of SARS-CoV-2 infection in the Lombardy Region.

Methods

For this systematic review, we searched the literature on April 2020 and then updated in August 2020, in order to identify data regarding incidence, mortality and hospitalizations by province and municipality, and the impact of the main containment and organizational measures. In addition, this report also analysed data on mortality due to COVID-19, hospital admission, analysis of administrative measures, and infections among healthcare personnel. Lastly, we also revised data regarding interregional and international comparisons, and serological and environmental data antecedent the notification of the first case (20 February 2020), with the aim to backdate the beginning of the epidemic.

The search was conducted on PubMed/MEDLINE and EMBASE, using the PRISMA 2020 checklist criteria(5). The following search terms were used: “coronavirus” (and synonyms) AND “Lombardy” (and synonyms, including the name of provinces). We used a broad search strategy not to lose potential interesting articles. No time filter was applied. Referring to the grey literature, the following data sources were assessed: web pages of all the Agenzie di Tutela della Salute (ATSs – Health Protection Agencies) of the Lombardy Region; various scientific foundations, the Lombardy Region website, the website of the Istituto Superiore di Sanità (ISS – National Institute of Health), including the epidemiological portal “Epicentro”, Website and Civil Protection Dashboard. Moreover, we also used Google as a search engine for any additional regional report using the following keywords: data epidemiology, serology, swabs, deaths, mortality, RSA, COVID, Lombardy, Milan, Bergamo, Brescia, Como, Cremona, Lecco, Lodi, Mantua, Monza, Pavia, Sondrio, Varese, differently combined among them.

The inclusion and exclusion criteria were set as follows: articles written in English or Italian which, within the title or the abstract, mentioned COVID-19 and at least one Lombard city that is the provincial capital. After eliminating duplicates, two investigators independently reviewed all abstracts. Disagreements between the authors were resolved by consensus. The reference lists of included articles were screened in order to identify further useful articles. A detailed description of methodology used, as well as the extensive report of data retrieved and results are reported in Supplementary material (Full report).

Results

Epidemiological data: incidence, testing and fatality rate

When considering incident rate, we noticed that the number of new cases already recorded in March 15th was extremely high in Lombardy, particularly in Lodi, Bergamo, Brescia, Cremona and Pavia provinces, with Lodi province the most affected (6). Tosi et al. (7) reported that Lombardy region carried out 230,000 diagnostic tests during the period 20 February - 15 April, with a ratio of positive cases to tests carried out of 27.9% - the highest among the 6 countries considered (Italy 17,800, Spain 17,500, France 5,000, Germany 16,900, United Kingdom 6,000, United States 10,000 per million). However, it should be considered that the testing policy strongly influences the probability of finding positive cases which in turn foster the general statistics on the progress of the disease. Indeed, at the beginning of the pandemic, the testing policy available in Lombardy, as in the rest of the countries, was not used on a large scale. Indeed, only symptomatic subjects were tested, highly underestimating the real incidence. Another element that has changed significantly during the pandemic is the case-fatality rate (CFR). In a study comparing the CFR in three different time points (two, four and six months after the beginning of the pandemic) showed an extreme variability with a significant increase in old age, also due to the presence of comorbidities (8). This phenomenon also explained why Italy, which has the highest average age in Europe, had a higher absolute number of

symptomatic (and therefore actually diagnosed) cases. Until 25th September 2020, the deaths attributed to COVID-19 in Lombardy region were 16,937 (47.3% of the national deaths attributed to COVID-19) (9). Tosi et al. (7) also estimated the Infection Fatality Ratio (IFR) for Lombardy that was 0.43% for the age group 0-70 years old, and 10.5% for subjects older than 70 years, whereas the overall value was equal to 2.19%. Furthermore, in this cohort of 5,484 close contacts, the risk of death from COVID-19 decreased significantly with the progress of the epidemic (-60% for subjects surveyed after March 16 compared to the previous period). The data is interesting, since the calculation of the IFR instead of the CFR can provide a more realistic estimate of lethality than just hospital cases or standard surveillance data (takes into account the symptomatic and asymptomatic or paucisymptomatic cases). A study shows that as of April 15 the lethality in Lombardy was 18.3%, higher than in Veneto where it was 6.4%, and a mortality (calculated considering the start date of the epidemic in each reality) lower than the other metropolitan areas and regions such as New York and Madrid (10). These data were also confirmed by two other articles that establish a comparison of the mortality figure at 30 and 70 days from the start of the epidemic between the Lombardy Region and other metropolitan regions similar in terms of demographic and socio-economic characteristics (11, 12).

Serological data

Seroprevalence surveys promoted by Lombardy region started on April 23, 2020 (13). Results showed that, 34% of the general population (58.3% Bergamo, 18.4% Milan, 41% Pavia, 38% Valpadana, 35% Brescia); and 13.5% of healthcare-workers developed antibody positivity (14). More in details, in Bergamo from April 23 to June 3, 2020, the positivity rate was 57% among the general population and 30% among healthcare-workers (15). In the territory of the Bassa Valle Seriana, till August 5, 2020, 48.8% were positive in Nembro, 42.6% in Albino and 34.8% in Alzano Lombardo (16). As of July 10, 2020, 10% of the population, in the Insubria area, was positive (17). Similar data were found for the Metropolitan City of Milan and the Province of Monza Brianza. On August 3,

2020, ISTAT (National Institute of Statistics), and the Ministry of Health, released the first results of the seroprevalence survey conducted from May 25 to July 15, 2020, in which seroprevalence in Lombardy was estimated at 7.5% (CI 95% 6.8-8.3) (18). Milani et al., analysing the blood of cohabitants of COVID-19 patients, found antibody positivity in 15% of subjects who apparently did not show symptoms (19). In Lodi, a study was performed on 300 blood bags collected between 27/01/2020 and 20/02/2020 - thus before the first case of Codogno - which found antibody positivity in 2% of cases, while analysing another 390 blood bags collected between 18/03/2020 and 6/04/2020 the percentage reaches 21% (20). Among the environmental surveillance tools, the monitoring of the viral load on wastewater samples is one of the most relevant, currently used for polio virus (21). A study conducted by the National Institute of Health found the presence of viral RNA in wastewater samples taken in the cities of Milan and Turin in December 2019 and late January 2020, respectively. These results allow for a safe back-dating of the circulation of the pathogen in Northern Italy (22).

Trend of ordinary and intensive care hospital admissions

Many scientific articles described how Lombardy hospitals adopted solutions for increasing the hospital capacity, involving various departments such as Neurosurgery (23), Cardiology (24), Physiatry and Rehabilitation (25), Radiotherapy (26), Transplant Surgery (27), Oncological Surgery (28), Orthopedics (29, 30), Nephrology (31), Urology (32), and Psychiatric Services (33). In Lombardy, also considering the intensive care beds in "Fiera Milano", reached a total of 13.72 beds per 100 thousand inhabitants during the peak of the epidemic corresponding to a total of +113.9% (from 723 on February 23 to 1547 on March 23, 2020) during the first 30 days of the epidemic (12).

Discussion and conclusions

From the analysed data it emerged that Lombardy was the first European region in which the virus began to circulate as early as January 2020 (and probably

even earlier). Although the high number of cases and deaths recorded since the beginning of the epidemic, the reproduction number observed in Lombardy Region was, at the beginning of March 2020, the same (or lower) than in other regions. This data shows how Lombardy Region has managed the implementation of containment and mitigation measures aimed at contrasting and / or delaying the epidemic, even in a time in which there was a lack of knowledge about transmission route (34), preventive measures (35), and best therapeutic approaches (36). Furthermore, by comparing the Lombardy Region with other demographically similar European and extra-European regions, it is shown that the mortality at 70 days from the beginning of the epidemic was lower compared to other analysed areas. In light of this, the implementation of significant and consistent containment actions were the main weapon to contrast and prevent the spread of the infection.

In conclusion, SARS-CoV-2 has spread rapidly around the world in the absence of effective and specific therapies. Data of the first epidemic wave in Lombardy, compared to other Italian and foreign regions, highlight the extreme criticality of having had the first autochthonous case (and the first substantial outbreaks) when knowledge was still scarce and individual prevention measures were not widespread. In this context, the implementation of health measures and global policies have become an urgent priority.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

Funding: This is part of the “Lombardy regional welfare to protect the elderly and chronic patients: impact of the COVID-19 emergency” project.

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Received: 15 September 2021

Accepted: 28 September 2021

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