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Empirical "integrated disease management" in Ferrara during the Italian plague (1629–1631)

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ABSTRACT

Plague, a highly infective disease caused by *Yersinia pestis* (Proteobacteria: Enterobacteriales), ravaged Europe from 1347 over the course of more than 450 years. During the Italian Plague (1629–1631), the disease was rampaging in the entire Northern Italy down to Tuscany, but the city of Ferrara was relatively spared, in spite that the economic activities were maintained with highly affected cities, such as Milan, through the relevant salt commerce.

The aim of the study is to evaluate the hygiene rules that were effective in preventing the spread of the plague in Ferrara in 1630, by examining historical documents and reports. According to these documents, a kind of empirical "integrated disease management" was carried out, using remedies including compounds with bactericidal, anti-parasite and repellent activity, and by technical strategies including avoidance of possible plague carriers. The anti-plague remedies and technical strategies used in ancient Ferrara are critically analysed using a multidisciplinary approach (pharmaceutic, medical, epidemiologic and entomological) and compared to current prevention protocols.

1. Introduction

Plague is known to be caused by *Yersinia pestis* (Proteobacteria: Enterobacteriales). The clinical forms of plague infection are two: bubonic and pneumonic. Bubonic plague is the most common form, characterized by painful swollen lymph nodes or buboes. Plague is transmitted between animals and humans by the bite of infected fleas, direct contact with infective tissue, or inhalation of infected respiratory droplets [1]. Besides being transmitted by the rat flea, *Xenopsylla cheopis* (Siphonaptera: Pulicidae), the disease may be transmitted by other flea species such as the human flea, *Pulex irritans* (Siphonaptera: Pulicidae). Fleas can be carried by several species of domestic or wild mammals [2–4]. Throughout the centuries, Italy was struck by many plague epidemics and very few cities were spared by the infection [5–7]. One of the most severe plague epidemics (the "Italian Plague") occurred from 1629 to 1631 in association with the war for the Mantuan Succession [5,7]. The aim of this study is to assess the prevention rules that were effective in preventing the spread of plague in the city of Ferrara in these years, while the disease was rampaging in the entire Northern Italy up to Tuscany. The study is based on historical documents, reports and public announcements, integrated into by recent literature on plague hosts, medical protocols, and antimicrobial, insecticide and repellent activity of compounds used as "rimedi" ("remedies") against plague at that time in Ferrara.

The city of Ferrara, established since 400 CE as a Roman garrison, became a town in 800 CE and rose to importance under the lordship of the House of Este, established since 1264. Under this dynasty Ferrara became one of the most important cities in Italy and Europe. The University was founded in 1391 by Alberto V d'Este by permission of Pope Boniface IX, and the city hospital (Ospedale Sant'Anna) in 1440 by permission of Pope Eugene IV. Students from all over Europe, among them Paracelsus, attended the University following the lectures in medicine and botany by renowned scholars such as Niccolò Leoniceno, Giovanni Manardi and Antonio Musa Brassavola. When the House of Este, devoid of legitimate heirs, ended in 1598, the government of Ferrara returned under the direct control of the Pope and the city was administered by a papal Legate. Although the importance of Ferrara as a Renaissance court declined, nevertheless the city continued to be a relevant commercial hub thanks to its proximity to Adriatic ports and Po River branches (Fig. 1) [8,9].

The city of Ferrara and its territory were repeatedly struck by plague and the main epidemics were in 1398, 1439, 1505 and 1528 [10]. After

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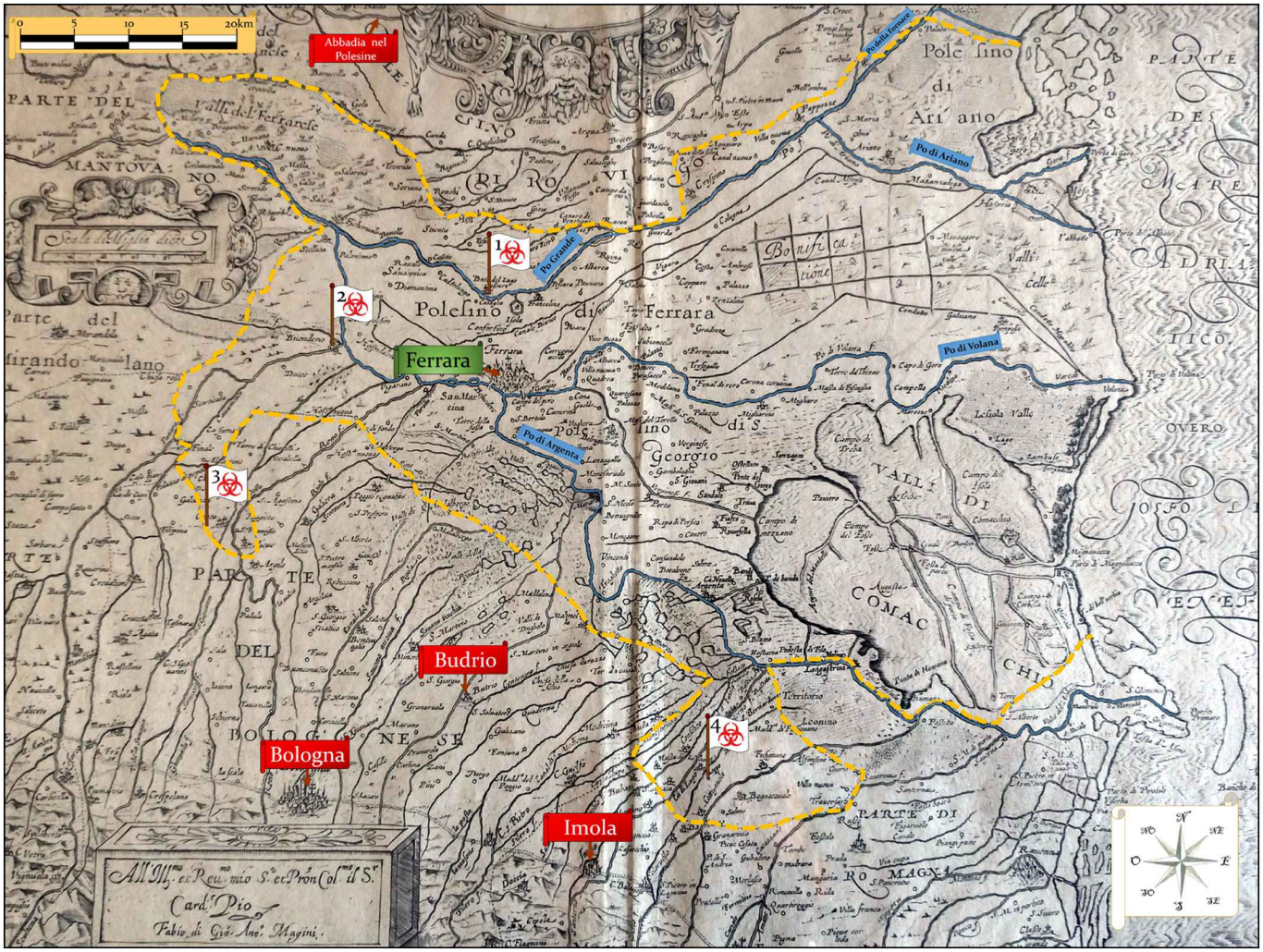

Fig. 1. Detail of a geographical map by Giovanni Antonio Magini [69] showing the papal Legation of Ferrara and the nearby territories. The yellow line shows the boundaries of the Legation and the small flags the locations struck by the 1629 plague. 1, Ponte di Lago Scuro; 2, Bondeno; 3, Cento; 4, Lugo. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the 1528 epidemics that killed 20,200 people in town [11] the Duke Alfonso I d'Este summoned the Spanish physician Pedro ("Pietro") Castagno, a renowned expert of plague management who had a recipe for a special oil ("*Composito*") against plague. Castagno provided Ferrara with competence in dealing with plague epidemics in Ferrara, establishing a series of health rules. Before his arrival, the only sanitary rules practiced in Ferrara were "health barriers" and "rimedi" ("remedies") devised by court and university physicians. During his service Castagno wrote a renowned manuscript, "*Reggimento contra peste*" ("Regimen against the plague"). After his death in 1569, the manuscript was printed by Castagno's son Giovanni Paolo and had many editions from 1572 to 1692 [12]. The 1572 edition of the book, published under orders by Alfonso Estense Tassoni, Judge of *Savi* (wise men), contained the rules for using the *Composito* and also the key sanitary rules to be practiced in the case of an outbreak. The rules contained in the *Reggimento* worked so well that all cases of plague ceased since 1576 in Ferrara and they were all enclosed in public proclaims and obligatory sanitary rules, even after the death of the author [13–15].

After the government changed from the House of Este to the papal Legation, about 32,000 citizens remained in Ferrara in 1601 [16]. In 1629 a new plague outbreak threatened Northern Italy [5]. According to the Report [17] in early November 1629 letters were brought from Venice to the health officers in Ferrara reporting that plague was spreading near Milan because of the invasion of Alemanni troops. The news was reported to the Pope's Legate, Cardinal Giulio Cesare Sacchetti, who planned measures against the epidemics. It is known that from 1629 to 1631 the plague ravaged many northern and central Italian cities, among which were Turin and Alessandria in Piedmont, Milan, Mantua, Cremona, Bergamo and Brescia in Lumbardy, Venice, Vicenza, Verona, Padua and Treviso in Veneto, Parma, Piacenza, Bologna, Modena in Emilia-Romagna and Florence, Pistoia and Lucca in Tuscany. Some locations near the legation of Ferrara, such as Abbadia nel Polesine (today Badia Polesine), Imola and Budrio, were also hit (Fig. 2) [5]. In Northern Italy, only Ferrara had not been affected by plague for years, due to its unique public rules.

2. Bibliographic methods

The historical part of bibliographic investigation about the plague epidemics in the years 1629–1631 was based on documents, books, reports and public announcements, while the scientific part concerned extant medical protocols, epidemiology and possible antimicrobial, insecticide and repellent activity of compounds whose use as "rimedi" ("remedies") against plague in Ferrara was documented.

For the historical part, books, reports, manuscripts and other documents, spanning several years, were consulted at the Biblioteca Comunale Ariostea (Municipal Library "Ariostea"), at the academic libraries of the University of Ferrara, at the Archivio storico comunale

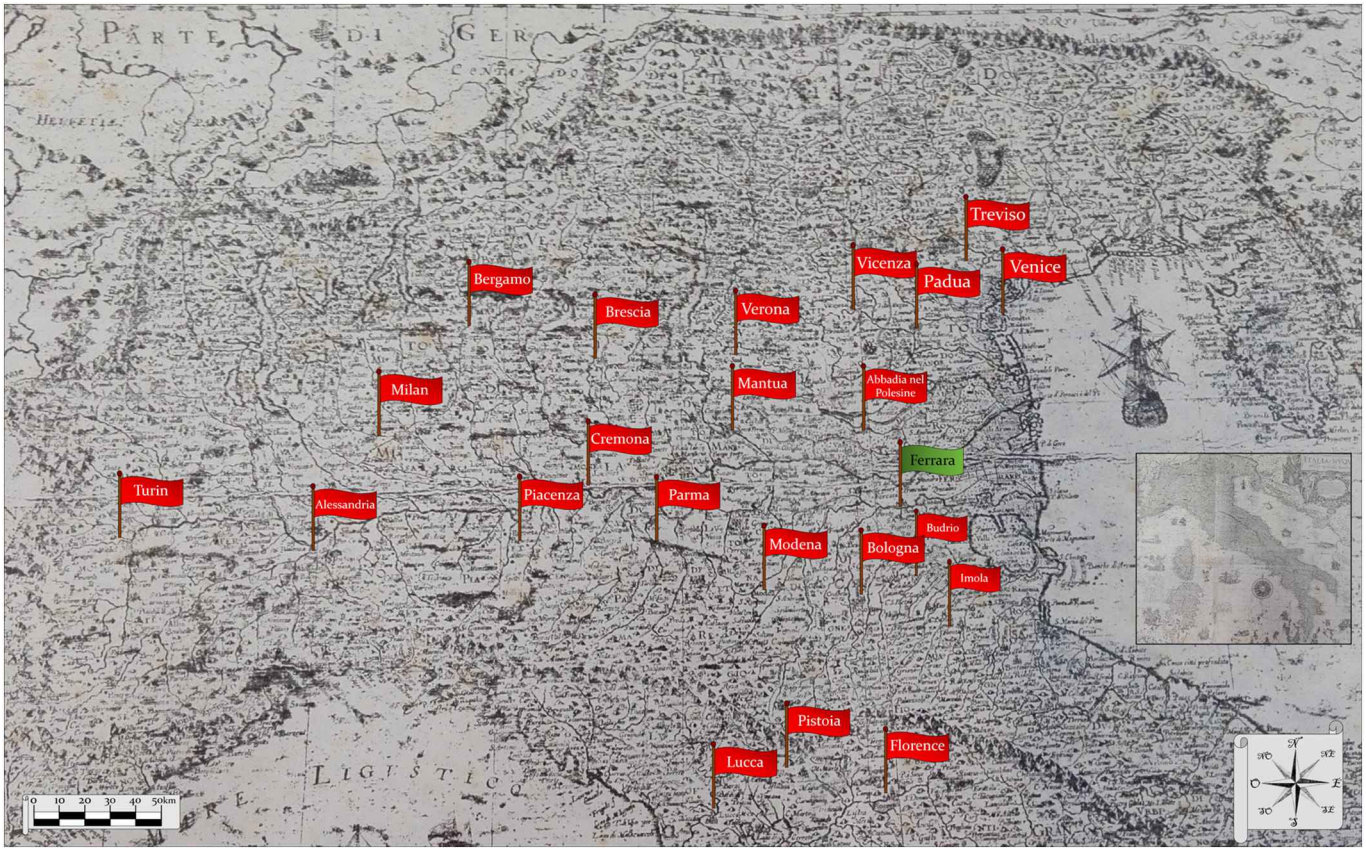

Fig. 2. Detail of a map of Italy by G. A. Magini showing Northern Italy and part of Central Italy [70]. The map reports the main Italian cities struck by plague from 1629 to 1631 (red flags). The green flag indicates the city of Ferrara which was spared by the epidemics. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(Historical Archives of the Municipality) and at the Archivio di Stato (State Archives), all in Ferrara (Italy).

For the scientific part, Internet sources such as PubMed, Scopus, SciFinder, Google Books (Advanced Book Search) and OPAC (Catalogue of National Library Service, Italy), were searched, as far as possible with no time and language limits. For each publication obtained via Web, either by interlibrary services or by a direct contact with the authors, the reference list was also checked to extend the search.

The main historical documents that allowed to assess the prevention rules that were effective in preventing the spread of plague in the city of Ferrara in 1630 were the following:

- "*Memorie di quanto s'è fatto per preservazione dalla Peste a Ferrara […] ne gli Anni 1629, 1630, 1631*" (Report about what has been done to protect Ferrara from the plague […] in the years 1629, 1630, 1631), henceforth "*Memorie*" [17]. This document contains the report and all public announcements made in Ferrara from 1629 to 1631;
- "*Ordini e auuertimenti ne' sospetti di peste*, 1623" (Orders and warnings about suspects of plague) [18], henceforth "*Ordini*".
- "*Reggimento contra peste*" (Regimen against plague), henceforth *Reggimento* written by Pietro Castagno, a Spanish physician summoned in Ferrara to fight plague. The book was originally a manuscript, later published in several editions since the 16th century [13–15].
- "*Tractato contra la peste*" (Treatise against plague) henceforth *Tractato*, written by Giovanni Manardi ("Manardo"), physician and professor at the University of Ferrara since 1482 [19].
- "*Annali delle epidemie occorse in Italia dalle prime memorie fino al 1850, Parte Terza dall'anno 1601 al 1700*" (Annals of the epidemics which occurred in Italy from the first record up to 1850, Third Part from the year 1601 to 1700), written by Alfonso Corradi, physician and professor at the University of Pavia [5].

3. Results and discussion

Based on the above historical documents, several factors contributed to a successful prevention of the spreading of the plague in Ferrara in 1630. Among them there were improvements in city construction, strict surveillance rules and strategies in the city and state borders for transit of people and traded goods, management of suspected plague cases, strict hygiene rules for city, public places and houses, personal hygiene and information about "rimedi" ("remedies") that were considered effective in protecting people from the infection. Each one of these factors will be examined in a dedicated paragraph.

3.1. Improvements in city construction

Construction improvements along the centuries contributed to the successful prevention of plague in Ferrara. Ferrara is known worldwide for its advanced urban planning ("Erculean Addition"), the first one in the Renaissance, commissioned in 1492 by Ercole I d'Este to the architect Biagio Rossetti [20]. However, since 1375 the city roads had been paved with firestones under the authority of Niccolò II of Este and the first sewer system was built in 1425 [21]. The urbanistic improvements provided better hygiene conditions for everyday life in the city and an easier way to identify and dispose of live and dead carriers of the plague.

3.2. Surveillance and control of people and traded goods

According to *Ordini*, the city maintained a state of continuous alert about plague, with a permanent surveillance team, the *Congregazione*

della Sanità (“Congregation for Health”), composed of authorities, noblemen, physicians and the apothecary of the Hospital [18].

In addition to the Pope's Legate and the Judge of *Savi* (wise men) the Congregation had among its permanent members eight *Gentiluomini* (“Gentlemen”) born in Ferrara. The Congregation also included a trader expert in foreign countries, borders and suspected cases of plague, and had two Presidents who were on duty for two years: the elder member was replaced by elections while the younger one remained to ensure continuity of service.

There were political networks with neighboring states including exchange of *Bandi* (“ordinances”) and news. Each traveler had to be equipped with *Fedi* (“proofs”), which certified his/her passage in localities free from suspicion of plague. Upon the entrance in Ferrara, the name of the Control Officer and of the Gate of entrance was written on the *Fedi*. The level of alert for plague was established through exchange of information and communications among cities. In the highest among the four levels of alert, the *Fedi* had to contain information ensuring personal identification. Concerning the personnel involved in the surveillance, in the first level of alert, when suspicion was low, a Deputy was enough for each city gate; in the second level, when suspicion was higher, two Gentlemen or Honorable citizens were added as reinforcement. In the third level, when suspicion was very high, an alert had to be issued to river and sea ports and passages. In the fourth level of alert, because the danger was considered near, a medical doctor had also to be present at the city gates [18].

Upon news of plague outbreaks, only two city gates were left open under strict surveillance, Porta San Paolo and Porta San Giovanni Battista (Fig. 3) [17]. The access to the city was then forbidden to beggars and gypsies and extremely severe penalties were inflicted to looters because to the danger of spreading the disease [17]. Equally rigid was the surveillance at the state borders. Local governors and *Podestà* (“Chief Magistrate”) had to recruit other four or six people as *Signori Conservatori* (“Keepers of Health”). Special attention was paid to merchandise, especially when it was transported along the river and by ships in ports. Regardless of the difficult situation during plague outbreaks, salt trade with Milan was kept active, using extreme precautions.

Special attention was paid to horse-drawn foreign boats in transit: ordinances were issued to unload salt at the borders, using designated wooden canals and operating under the highest prudence. It is interesting to notice that health control practices usually performed in river docks had been dismissed everywhere except in Ferrara [18]. However, the situation got almost out of control in August 1630 at the southern border at *Ponte di Lago Scuro* (today Pontelagoscuro) (Figs. 1 and 4): some suspect deaths were concealed to avoid interference with commercial interests concerning river transported merchandise such as oil and mill products (*Bando 68. 28 agosto 1630, Sospensione di Ponte di Lago Scuro*) [17].

Problems occurred at the state borders. In the small town of Bondeno, there were cases of plague due to illiteracy of controllers [17]. The city of Cento, near Ferrara, was severely affected by the plague, counting about 6000 deaths including five doctors who attended sick people in the lazaret. In the city of Lugo, near Ravenna, the Governor failed to report certified cases of plague, thus the city was ravaged with about 6000 deaths, including the Governor himself [5,17] (Fig. 1). According to *Memorie*, the economy was carefully supervised

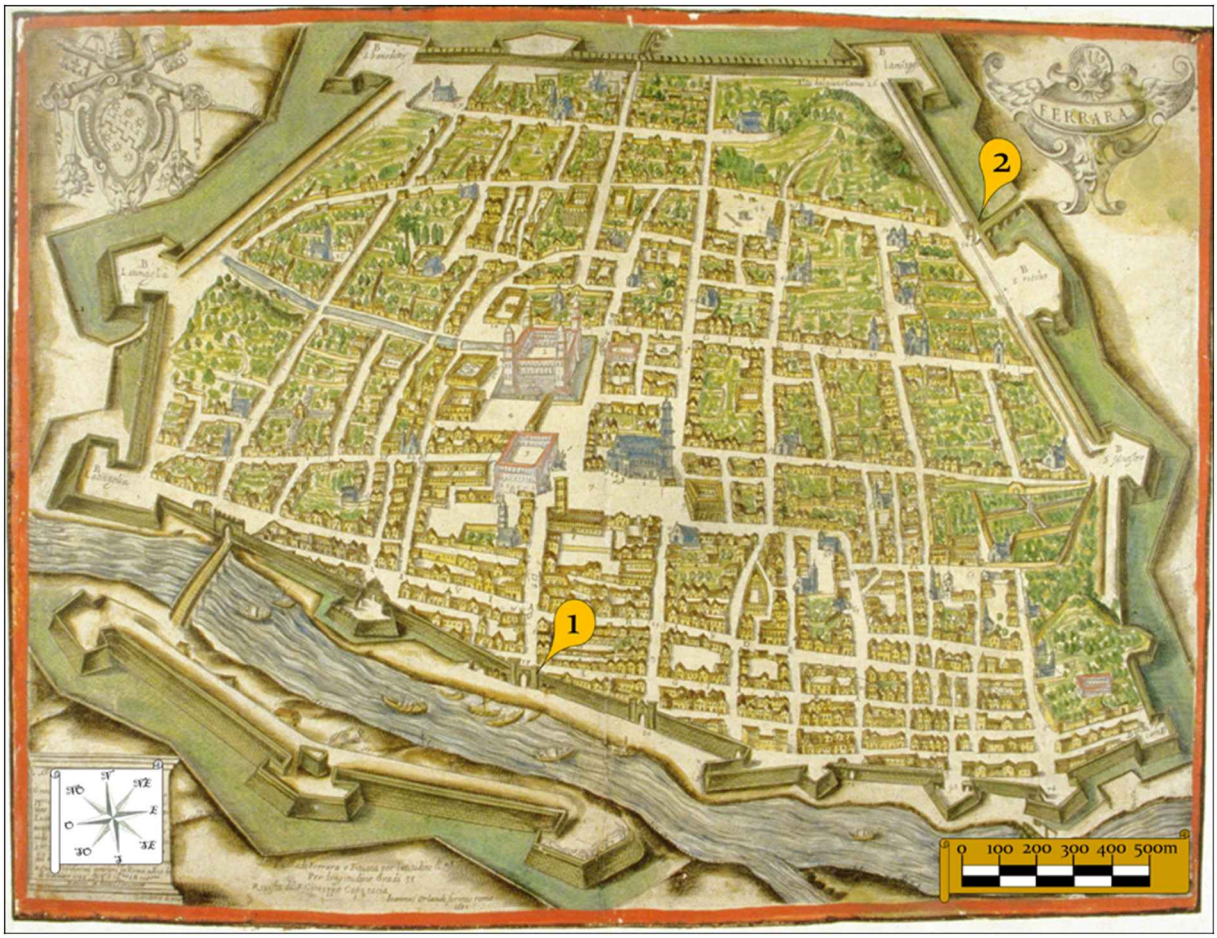

Fig. 3. City of Ferrara [71] at the beginning of XVII century. The map of the city indicates the only two gates which were kept open upon news of plague outbreaks: 1, Porta San Paolo; 2, Porta San Giovanni Battista.

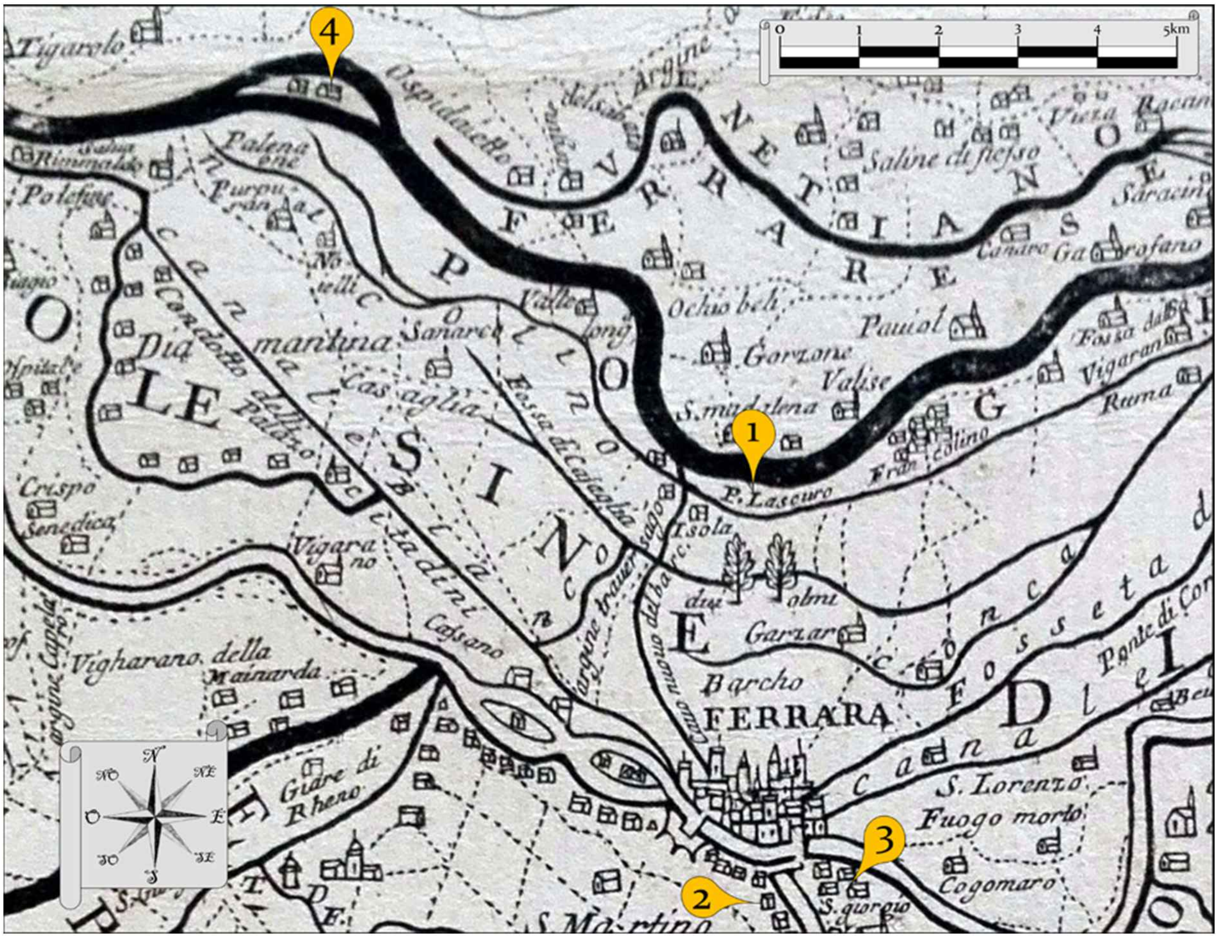

Fig. 4. City of Ferrara and its surroundings [72] at the beginning of XVII century. The map indicates the positions of the lazarets, of which two were operative (1, Ponte di Lago Scuro; 2, Borgo San Luca), two supplementary (3, monastery of the Olivetans in San Giorgio and ship dockyards) and one planned (4, island of Bonello).

and money was not wasted. From November 1629 to June 1631, a very high amount of money (50,000 *scudi*) was spent on preventative health measures [17].

3.3. Management of suspected cases

In order to protect the city from the infection, the authorities decided that the only way to stop the plague was to immediately identify the disease, always considering each case as suspect and potentially infectious [18].

According to *Memorie*, in all cases of suspected infection individuals and all people who had contacts with them were immediately isolated in one of the two city lazarets [17]. The first lazaret was established in Borgo San Luca, immediately outside the city walls, and the second one in *Ponte di Lago Scuro*, about 5 km from the city walls. Moreover, the monastery of the Olivetans in San Giorgio was preventively supplied with hundreds of beds and the ship dockyards along the southern branch of the river were adapted as hospital rooms (Fig. 4). In 1629, the threat of large numbers of plague victims led to a plan to establish another lazaret at about 15 km from the city, in Bonello, a large island on the Po River (Fig. 4).

In the first case of infection in Ferrara, involving Bartolomeo Rossi, a postal employee, the isolation and decontamination of his house were sufficient to limit the contagion. The intervention was more complex in the case of a boy attending school: in addition to preventative routine procedures, schools were closed on 20 September 1630, extending closure to the end of October until the holiday season (*Bando 74, 20 settembre 1630, Sopra un caso successo in Ferrara, sospensione delle Scole de Putti; Bando 85, 29 ottobre 1630, Proroga della proibizione delle scole*) [17]. Special attention was paid to poor and incurable people, who were supported at public expense so they would not contribute to the spread of the disease.

3.4. Hygiene rules

Hygiene rules in the city, public places, houses and everyday life, described in detail in historical documents, were a key issue in preventing plague spreading in Ferrara.

Concerning public hygiene, great attention was paid to the cleanliness of the city. First of all, dogs, cats, chickens and pigs were identified as directly involved in the transmission of plague because they were considered "filthy" ("*immondi*"). It was prohibited to raise animals such as pigs (*Bando 92, 27 marzo Nuove provvigioni, & ordini per tener netta la città; Bando 58 13 luglio Proibizione di tener Porci, & altri animali immondi nelle Città*) [17], or other animals causing excessive dirt, such as silkworms (*Bando 39, 8 giugno 1630, Sopra le Caldarane per i loro vermi, che cauano dalla seta; Bando 98, 12 maggio 1630, Sopra i letti de Caualieri, e vermi, che si cauano dalla seta)* [17]. It was mandatory to spread large amounts of *calcina* (lime) on materials suspected to be contaminated, burning (without touching them) the rags found in streets and burying carcasses of dead dogs, cats and chicken [17]. Another ordinance raised attention on uncontrolled stray dogs (*Bando 53, 6 luglio 1630, Sopra l'andare i Cani sciolti*) [17].

In the first printed edition of the *Reggimento*, published in 1572, it was stated that materials that had been in contact with sick people had to be burned to prevent contact by dogs or cats, which could carry the

plague inside healthy homes [14]. Concerning the way of transmission of plague by the rat flea, *X. cheopis*, it is interesting to notice that rats were never mentioned among "filthy" animals. Nevertheless, robes for city authorities (including physicians) were made of oilcloth "*tele incerate, ò di Sangallo*" to prevent fleas from clinging to clothes [17]. However, plague may be transmitted by other flea species, for example by the human flea *P. irritans*, which may also colonize short haired mammals such as pigs, and the fleas of cats *Ctenocephalides felis* (Siphonaptera: Pulicidae) and dogs, *C. canis* [3,22,23]. The prevention rules established in Ferrara may therefore have been effective in interfering with the activity of plague vectors.

It is interesting to notice that lime, used to treat infected materials in Ferrara, was also widely used against plague and other diseases [24,25].

Special care was paid to everyday hygiene rules and cleanliness in houses. In order to *smorbare le case* ("sanitize houses"), all worthless furnishing had to be burned, throwing away all dirty or cracked items and making a bright fire in the middle of the house. Perfumes had to be spread in the house for fifteen days, valuable objects had to be washed and slightly heated, and money had to be warmed in a fire. Meanwhile, wool, leather clothes and lining had to be hanged up in the sun, beaten with a stick in the evening, dried near a fire and perfumed, to make them clean and tidy [18]. When clothes and linings are exposed to the sun and beaten with a stick, it is likely that adult fleas are expelled. It is known that larvae exposed to direct sunlight quickly die, being sensitive to heat and dehydration [26]. Probably the act of warming clothes near a fire is another effective way to get rid of immature fleas.

The effects of temperature and humidity on developmental stages of two flea species, *Synopsyllus fonquerniei* (Siphonaptera: Pulicidae) and *X. cheopis*, responsible for transmission of plague, have been confirmed: high temperature and low humidity have a negative effect on development [27], so the rule of avoiding humidity in houses and warming people and clothing to a fire could have been effective. Linen clothes had to be washed with special herbs (*Lauro, Menta & Artemisia*, probably laurel, mint and sagebrush) in *liscivo* (lye), and once dry they had to be perfumed [13]. Laurel (*Laurus nobilis*) and several species of the genera *Artemisia* and *Mentha* have been traditionally used in laundry for their insecticidal/repellent properties [28,29] (Table 1). Literature data show that 1,8-cineole, thujone and camphor are the major components in many essential oils of different species of the genus *Artemisia* (sagebrush). The sagebrush oil not only has antimicrobial activity, but it is also an insect repellent due to the presence of sesquiterpenes [30,31].

Living quarters had to be kept well ventilated, free from dust, cobwebs and humidity by lighting a *fuoco chiaro* (a high temperature fire) and burning scented wood logs of *ginepro, lauro, sarmenti di vite* (juniper, laurel and vine shoots) [13]. The insecticidal and insect-repellent efficacy of juniper (*Juniperus communis*), whose major components are α-pinene, α-terpinene and linalool [32], is well known and also reported in veterinary medicine [33]. Similar properties have been reported for laurel and its fumigations [28] (Table 1). No insecticidal activities have been reported for vine shoots.

When someone was ill, clothes and bed linen had to be changed often, a bright fire had to be made in the room and the room had to be ventilated [13]. Wastes from the patient had to be carried out in the open and burned as stubble; they had not to be touched by dogs or cats. No object belonging to the patient had to be carelessly thrown away, but they had to be covered with *calcina sfiorata, che questa estinguerà il veneno* ("lime, because in this way the venom could be extinguished").

3.5. "Remedies" and personal hygiene

The 1623 edition of the *Reggimento* contained the rules for the use of a special oil against plague, the *Composito* [18], developed by Castagno, who built his fortune on it. The *Composito* had always to be ready, stored in a box located into a wall in the Municipality palace, locked with two different keys, one held by the Judge of *Savi* and the other by the *Speziale* (apothecary). The recipe of the *Composito* was not reported but only its use: "Before getting up in the morning, after lighting a fire of scented woods (juniper, laurel and vine shoots), warm the clothes and above all the shirt, rub first the heart region, near the fire to ease balm absorption, then the throat". Afterwards, "wash hands and face with *acqua chiara* (clean water) mixed with wine or vinegar of roses, with which sometimes all body should be cleaned, using a sponge".

The *Composito* was administered through anointing in various body parts, but also per os ("by mouth"), although in this case its efficacy was dubious.

Although the formula of *Composito* was secret, a list of raw materials ordered by Castagno to make the *Composito* was found in Ferrara [12]. Examining the list, there is a great correspondence with the formula for "*olio di scorpioni*" published in 1544 by the Senese physician and botanist Pietro Andrea Mattioli. In addition to scorpion venom and others ingredients, the *Composito* by Castagno also included the viper [12]. Peptides of the scorpion venom are known to have antibacterial activity [34] (Table 1) and the same activity has been reported for viper venom [35], Nevertheless, we can not exclude that the peptide components of *Composito* may have undergone major changes during the galenic preparation.

Other components of the *Composito* were *mirra fina, reubarbaro elletto, zedoaria, croco, aristologra longa*. Some of these components and of other remedies have been examined for insecticide and repellent activity towards vectors of plague and other diseases, based on recent literature data.

Antibacterial activity has been reported for *mirra* (myrrh, *Commiphora myrrha*) [36], *reubarbaro* (*Rheum* spp.) [37], *zedoaria* (zedoary, *Curcuma zedoaria*) [38], *croco* (*Crocus sativus*) [39] and *aristologra* (*Aristolochia* spp.) [40]. Repellent activity against insects has been reported for zedoary [41,42]. Crocin and safranal are two important bioactive components in *C. sativus*. Some semi-synthetic derivatives of safranal were tested to establish which modifications of chemical structure could improve the biological activity [39] (Table 1). As far as we may presume about the components, a two-action formula would have resulted, active on both the bacterium and the vector.

Another widely employed "rimedio" ("remedy") against plague was vinegar. Some barrels of high quality flawless vinegar were kept in the Municipality palace of Ferrara to be used in the case of plague, under the supervision of the Judge of *Savi* and the Keepers of Health. Great care was taken in guarding the vinegar barrels and in reminding the Judge of *Savi* to regularly inspect and refill them.

Acetic acid and vinegar have been recently reconsidered for antibacterial activity: they have been proved effective as tuberculocidal agent and active against food-borne bacterial pathogens, including *Escherichia coli* and *Salmonella enterica* (Enterobacteriales: Enterobacteriaceae) [43–46]. Acetic acid with antimicrobial activity may represent an alternative to common local antiseptics. In Ferrara vinegar was used undiluted to impregnate sponges to be kept in front of the mouth, for hand washing, for hand ablutions, as disinfectant for unclean objects such as money and in anti-plague mixtures. The traditional habit of washing hands with vinegar, or throw citrus peels on stoves or fireplaces, has been practiced until recent times. Antiseptic properties are traditionally attributed to vinegar, citrus, gentian and rue, and the common practice of wetting hands, face and body could have built a sort of barrier against the plague bacterium and the vector.

Personal hygiene at that time in Ferrara was unusually mandatory and performed by ablutions, daily linen changes and diffusion of scents in rooms. Antiseptic effects were achieved by wetting hands and face with vinegar, or by brushing a sponge all over the body. Vinegar was used alone or as *aceto rosato* (rose vinegar), in a mixture with *acqua rosa, e vin bianco* (rose water and white wine) added with *Carlina, Genziana, radice di Ruta Capraria, detta Giarga, Scorza di Cedro, Gedoaria* [13]. The mixture was recommended for hygiene of hands and body, but also for oral administration through a few drops. The genus name *Carlina* honors the Holy Roman Emperor Charlemagne or, according to

Table 1
Past and present medical remedies possibly active against plague bacterium and vectors.

Ingredients and galenic formulations							Ingredients, plants or plants of the same genus whose activity is mentioned in literature		
	Reggimento contra peste				*Manardo's remedies*			Antimicrobial activity	Insecticidal/Repellent activity
	Oil	Ablution	Laundry	Fumigant	Small bags/Scent-balls				
					Winter formulation	Summer formulation			
Aceto		•			•(AI)	•(AI)	Vinegar, acetic acid	[43–46]	
Scorpione	•						Scorpion venom	[34]	
Vipera	•						Viper	[35]	
Rabarbaro	•						*Rheum* spp.	[37]	
Carlina		•					*Carlinae radix*	[47]	
Genziana		•					*Gentiana lutea*	[48]	
Ruta capraria, Giarga		•					*Galega officinalis*	[49]	
Scorza, cortice cedro		•				•	*Citrus medica*	[50]	
Sandali citrine						•	*Santalum album*	[59]	
Benzoino						•	Benzoin/styrax	[60]	
Aristologra	•						*Aristolochia* spp.	[40]	
Ginepro				•			*Juniperus communis*		[32,33]
Lauro			•	•			*Laurus nobilis*		[28]
Menta			•				*Mentha pulegium*		[28]
Garyophili					•		*Eugenia caryophyllata*		[51,52]
Mirto						•	*Myrtus communis*		[28,61]
Camphora						•	*Cinnamomum camphora*		[62]
Artemisia			•				*Artemisia absinthium*	[30,31]	[28,29]
Mace					•	•		[54,55]	[53]
Nuce muscata					•		*Myristica fragrans*		
Cinnamomo					•		*Cinnamomum* spp.	[56,57]	[58]
Mirra	•						*Commiphora myrrha*	[36]	
Zedoaria	•	•					*Curcuma zedoaria*	[38]	[41]
Croco, Zafrano	•				•	•	*Crocus sativus*	[39]	

(AI): additional ingredient.

other authors, Charles V. The emperors were said to have used the plant against the plague for their soldiers. Antimicrobial properties have been reported for *Carlina* (*Carlinae radix*) [47], *genziana* (*Gentiana lutea*) [48], *ruta capraria* (goat's rue, *Galega officinalis*) [49] and *scorza di cedro* (cedar, *Citrus medica*) [50]. Moreover, significant antimicrobial effects have been reported for essential oil and decoction of *G. officinalis*, supporting its use in ethnomedicine [49].

Mangiferin, isogentisin and gentiopicrin were isolated from methanolic extracts of flowers and leaves of *G. lutea*. The synergistic activity of these compounds may be responsible for the positive antimicrobial effects reported for its the extract [48]. *Gedoaria* (zedoary) combines repellent efficacy [41] with antimicrobial activity [38] (Table 1).

Other popular “rimedi” (“remedies”) against plague cited in the *Reggimento* were *palle contra peste* (“scent-balls against plague”) to be smelled. Their composition was secret.

In the *Tractato* [19] published in 1522 (a translation into Italian of a Latin original by Giovanni Manardi) the preventive remedy suggested against the plague were the *sacheti* (“small bags”) and *balle* (scent-balls), probably with a similar composition with those of the *Reggimento*. The bags containing scents had to be placed above the heart, liver, stomach and genitals.

The bag to be used in winter (*Quella del verno*) contained *storace, iride, garyophili, mace, nuce muscata, cinnamomo, zafrano, ambra, muschio*. *Garyophili* (clove oil from *Syzygium aromaticum*, syn. *Eugenia caryophyllata*) has been reported as acaricidal on house dust mites by direct contact [51]. Clove oil in its major components (eugenol and β-caryophyllene) has repellent activity also towards body lice (*Pediculus humanus*, Anoplura: Pediculidae) [52]. *Nuce muscata* and *mace* (essential oils of seeds, nutmeg, and aril of *Myristica fragrans*) have recently shown adulticidal activity against *Aedes aegypti* [53]. Myristicin and trimyristin, components of *M. fragrans*, have shown antibacterial activity [54]. Ethyl acetate and ethanol extracts of *M. fragrans* have been successfully tested as new natural agents for oral care products against cariogenic and periodontopathic bacteria [55].

Cinnamomo (cinnamon oil from *Cinnamomum* spp.) has antibacterial activity on both Gram-positive and Gram-negative bacteria [56,57] and could be used as agent for microencapsulation in insect-resistant films for food packaging [58]. *Zafrano* (*C. sativus*) is known as antimicrobial [39].

The bag to be used in summer (*Quella dala Estate*) contained pulverized *ambre giale, foglie di mirto, cortice di cedro, fiori di nenuphare, rose, viole, zafrano, mace, sandali citrine, camphora, ambra, benzoi, muschio* [19].

Ambra (ambergris from *Physeter macrocephalus*) and *muschio* (musk from *Moschus moschiferus*) are scents obtained from animal sources. *Ambre giale* correspond to fossilized tree resin. *Cortice di cedro* (cedar fruit peel, *C. medica*) [50], *sandali citrine* (sandalwood, *Santalum album*) [59], *benzoi* (benzoin) [60], *mace* (aril of *M. fragrans*) and *zafrano* (*C. sativus*) are all known as antimicrobial. In *C. medica* oil, limonene and camphene are the main components and their observed antimicrobial activity supports traditional uses as food preserving agents [50].

Mirto (myrtle, *Myrtus communis*) is known as insecticide and insect repellent [28], with a specific repellent activity against *P. irritans* [61].

Essential oils from leaves, twigs and seeds of *camphora* (*Cinnamomum camphora*), have shown insecticidal and repellent activity, especially for one of its components, linalool [62] (Table 1).

The components of Manardi's *sacheti* were the basis of the corresponding scent-ball formulations, *Balle del Verno e dala Estate*. The scent-ball was made of perforated cypress or ash wood which contained a sponge soaked in a mixture of the cited substances and *aqua Rosata & Malvasia* (rose water & Malmsey wine) & *mezza parte di aceto* (“half

Table 2
Comparison between the present guidelines provided by World Health Organization against plague outbreaks and the guidelines practiced in Ferrara during the Italian Plague.

World health organization guidelines	Rules and methods of prevention in Ferrara
Prevention […] take precautions against flea bites and not to handle animal carcasses. […]	- Small bags (*sacheti*), scent-balls (*Balle contra peste*), oil (*olio contra peste*) fumigants (possible insecticide/insectorepellent agents). - Spreading of lime (*calcina*) on carcasses suspected to be contaminated. - Burning rags. - Avoid handling carcasses of dead dogs, cats and chicken, and bury them.
Managing plague outbreaks […] Disinfection. Routine hand-washing is recommended with soap and water or use of alcohol hand rub. […] Larger areas can be disinfected using 10% of diluted household bleach (made fresh daily). Ensure safe burial practices. Spraying of face/chest area of suspected pneumonic plague deaths should be discouraged. The area should be covered with a disinfectant-soaked cloth or absorbent material.	- Recommendation of frequent washing of hand and body with possibly antiseptic lotions. - Cleaning objects with mixtures with possible disinfecting activity. - Washing clothes with laundry lye added with herbs, - Careful cleaning of houses, keeping them ventilated and warmed by fire at high temperature, burning scented wood logs. - Exposing valuable objects to high temperature. - Spreading of lime on materials suspected to be contaminated.
Surveillance and control […] In order to effectively and efficiently manage plague outbreaks it is crucial to have an informed and vigilant health care work force (and community) to quickly diagnose and manage patients with infection, to identify risk factors, to conduct ongoing surveillance, to control vectors and hosts, to confirm diagnosis with laboratory tests, and to communicate findings with appropriate authorities. [...]	- Strict controls at the borders and gates of the city through a well-structured organization permanently settled and fully operative under alerts. - Strict supervision in the city that no suspect case could be concealed. - Presence of a medical doctor at the city gates at the highest level of alert. - Treatment of any suspect case as actual plague.
Managing plague outbreaks Find and stop the source of infection. Identify the most likely source of infection in the area where the human case(s) was exposed, typically looking for clustered areas with large numbers of small animal deaths. Institute appropriate infection, prevention and control procedures. Institute vector control, then rodent control. Killing rodents before vectors will cause the fleas to jump to new hosts, this is to be avoided. Isolate patients with pneumonic plague. Patients should be isolated so as not to infect others via air droplets. Providing masks for pneumonic patients can reduce spread.	- Raise alert upon small animal deaths. - Correct management and disposal of animal carcasses. - Institution of lazarets. - Employing daily substances with possible insect-repellent, insecticide and antiseptic activity: scent-balls and small bags with herbs and essences, rose water, vinegar, wine, and sponges soaked in vinegar. - The scent-balls, the small bags and the sponges could also have worked as a sort of “mask” to protect airways.

amount of vinegar). It was held in the hand for smelling, but it could also be shaken on the hands, rubbing the liquid on the face. These scent-balls could have exerted some antibacterial activity towards airways and possibly block the diffusion of infected aerosol. The same activity was probably exerted by vinegar used to impregnate sponges to be kept in front of the airways.

3.6. Studies on plague epidemics

Several studies have addressed the epidemics of plague in Italy and Europe from different points of view including epidemiology, economy and public health organization [6,7,25,63–67].

General preventative measures against epidemics, such as health magistrates and quarantine procedures, were commonly attempted along the centuries [24,63,64,66]. As previously mentioned, Ferrara succeeded in controlling plague since 1576 [12,14]. An interesting attempt to control the plague outbreak of 1582–1583 through sanitary rules was that by Protomedicus Quinto Tiberio Angelerio in Alghero (Sardinia), which had about 4000 inhabitants at that time [6]. However, Angelerio's rules had only limited success because of inactivity from authorities and hostility from the population about a required commercial block [6]. The relevant difference between the case of Alghero and that of Ferrara is the fact that the preventative measures established in Ferrara in 1629–1630 were able to protect not only a city of about 32,000 inhabitants, but also the entire territory of the papal legation, including all towns and villages inside it, and the measures were effective while the entire Northern Italy was the battlefield for the war of Mantuan Succession.

4. Conclusions

Since the second half of the 16th century, the city of Ferrara managed to undertake effective actions to limit the spreading of the plague (severe sanitary controls, treatment of any suspect case as actual plague and careful hygiene measures), simultaneously safeguarding commercial business and city economy. Ferrara was also preserved from the plague of 1630, cited by Alessandro Manzoni, which spread rapidly through all Northern Italy up to Florence.

Economy was carefully supervised and money was not spared neither wasted. Authorities in Ferrara believed that the only way to stop the plague was to immediately identify the disease, considering each case always as suspect and contagious, and providing certificates to others states in these situations. The methods applied in Ferrara were later praised as effective against plague by the renowned English physician Richard Mead [21,68].

The empirical and cooperative “integrated disease management employed in Ferrara during the Italian Plague (1629–1631) is similar to the rules of prevention, surveillance and control recommended by World Health Organization (WHO) [1] to manage plague outbreaks (Table 2).

In order to protect the city of Ferrara and its surroundings from the rampaging infection, the key factors were the awareness of the role of dogs, cats, chicken and pigs in the transmission of plague and the development of “rimedi” (remedies), whose components have been recently shown to have antibacterial, insecticidal and insect repellent activity (Table 1).

This study represents a base for further investigations on components of these remedies that exhibit some insecticide and repellent activity towards vectors of plague and other diseases, within a dedicated project of the University of Ferrara. As reported by WHO [1] from 2010 to 2015 there were 3248 cases of plague reported worldwide, including 584 deaths. Nowadays, plague is easily treated with antibiotics and the use of standard precautions to prevent acquiring infection. Historical remedies practiced in Ferrara during the Italian plague to protect the city could surprisingly represent an innovative research field aimed to prevention of dangerous emerging diseases.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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