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Empirical “integrated disease management” in Ferrara during the Italian Plague (1629-1631)

--Manuscript Draft--

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Abstract:	<p>Plague, a highly infective disease caused by <i>Yersinia pestis</i> (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evaluate the hygiene rules that were effective in preventing the spread of the plague in Ferrara in 1630, by examining historical documents and reports.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.</p>
Suggested Reviewers:	Oliver Sparagano olivier.sparagano@northumbria.ac.uk Renowned expert in the field Giovanni Cipriani giovanni.cipriani@unifi.it Renowned expert in the field Katharina Kreppel Katharina.Kreppel@glasgow.ac.uk Renowned expert in the field
Opposed Reviewers:	
Response to Reviewers:	Authors' Response to Reviewers First of all, we would like to thank the Editors and the Reviewers for their expertise and careful revision of the manuscript and for their useful comments and/or suggestions. The corrections made according to the suggestions by Reviewer n. 1 are indicated in yellow and those made according to the suggestions by Reviewer n. 2 are indicated in blue. Other corrections are indicated in green. Reviewer n. 1

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Dear Editors,

thank you very much for your mail concerning the manuscript “Empirical “integrated disease management” in Ferrara during the Italian Plague (1629-1631)” (PARINT_2019_279R1) by Vicentini et al., submitted to Parasitology International.

We wish to thank you and both Reviewers for your favourable comments and valuable suggestions.

We revised the manuscript according to the Reviewers’ comments, highlighting in yellow the changes made according to the suggestions by Reviewer n. 1 and in blue those made according to the suggestions by Reviewer n. 2. Other corrections are indicated in green. The answers to the Reviewers’ comments are enlisted below.

We hope now that our manuscript is suitable for publication on Parasitology International.

Thank you very much for your kind attention and best wishes.

Marco Pezzi, PhD
Dep. of Life Sciences and Biotechnology
University of Ferrara

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Empirical “integrated disease management” in Ferrara during the Italian Plague (1629-1631)

Chiara Beatrice Vicentini¹, Stefano Manfredini¹, Donatella Mares¹, Teresa Bonacci², Chiara Scapoli¹, Milvia Chicca¹, Marco Pezzi^{1,*}

¹Department of Life Sciences and Biotechnology, University of Ferrara, Via Luigi Borsari 46, 44121, Ferrara, Italy

²Department of Biology, Ecology and Earth Science, University of Calabria, Via P. Bucci, 878036 Arcavacata di Rende, Cosenza, Italy

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1 **Abstract**

2 Plague, a highly infective disease caused by *Yersinia pestis* (Proteobacteria: Enterobacteriales),
3 ravaged Europe from 1347 over the course of more than 450 years. During the Italian Plague (1629-
4 1631), the disease was rampaging in the entire Northern Italy down to Tuscany, but the city of Ferrara
5 was relatively spared, in spite that the economic activities were maintained with highly affected cities,
6 such as Milan, through the relevant salt commerce.

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

14

15 **Keywords:**

16 Italian plague; Ferrara; Integrated disease management; antimicrobial insecticidal repellent agents;
17 physical agents

18

19 **1. Introduction**

20 Plague is known to be caused by *Yersinia pestis* (Proteobacteria: Enterobacteriales). The clinical
21 forms of plague infection are two: bubonic and pneumonic. Bubonic **is** plague in the most common
22 form, characterized by painful swollen lymph nodes or buboes. Plague is transmitted between animals
23 and humans by **the** bite of infected fleas, direct contact with **infective tissue**, **or** inhalation of infected
24 respiratory droplets [1]. Besides being transmitted by the rat flea, *Xenopsylla cheopis* (Siphonaptera:
25 Pulicidae), the disease **may** be transmitted by other flea species such as the human flea, *Pulex irritans*.
26 Fleas **can** be carried by several species of domestic or wild mammals [2-4]. **Throughout** the centuries,
27 Italy was struck by many plague epidemics and very few cities were spared by the infection [5-7].
28 One of the most severe plague epidemics (the “Italian Plague”) occurred from 1629 to 1631 in
29 association with the war for **the Mantuan** Succession [5,7]. The aim of this study is to assess the
30 prevention rules that were effective in preventing the spread of plague in the city of Ferrara in these
31 years, while the disease was rampaging in the entire Northern Italy up to Tuscany. The study is based
32 on historical documents, reports and public announcements, integrated **into** by recent literature on
33 plague **hosts**, medical protocols, and antimicrobial, insecticide and repellent activity of compounds
34 used as “rimedi” (“remedies”) against plague at that time **in Ferrara**.
35 **The city of Ferrara**, established since 400 A.D. as a Roman garrison, became a town **in** 800 A.D. and
36 rose to importance under the lordship of the House of Este, established since 1264. Under this dynasty
37 Ferrara became one of the most important cities in Italy and Europe. The University was founded in
38 1391 by Alberto V d’Este by permission of Pope Boniface IX, and the city hospital (Ospedale
39 Sant’Anna) in 1440 **by permission** of Pope Eugene IV. Students from all over Europe, among them
40 Paracelsus, attended the University following the lectures in medicine and botany by renowned
41 scholars such as Niccolò Leonicensi, Giovanni Manardi and Antonio Musa Brassavola. When the
42 House of Este, devoid of legitimate heirs, ended in 1598, the government of Ferrara returned under
43 the direct control of the Pope and the city was administered by a papal Legate. Although the
44 importance of Ferrara as a Renaissance court declined, nevertheless the city continued to be a relevant
45 commercial hub thanks to its proximity to Adriatic ports and Po River branches (Fig. 1) [8,9].
46 The city of Ferrara and its territory were repeatedly struck by plague and the main epidemics were in
47 1398, 1439, 1505 and 1528 [10]. After the 1528 epidemics that killed **20200 people in town** [11] the
48 Duke Alfonso I d’Este summoned the Spanish physician Pedro (“Pietro”) Castagno, a renowned
49 expert of plague management who had a recipe for a special oil (“*Composito*”) against plague.
50 Castagno provided Ferrara with competence in dealing with plague epidemics in Ferrara, establishing
51 a series of health rules. Before his arrival, the only sanitary rules practiced in Ferrara were “**health**
52 **barriers**” and “rimedi” (“remedies”) devised by court and university physicians. During his service
53 Castagno wrote a renowned manuscript, “**Reggimento contra peste**” (“**Regimen against the plague**”).
54 After his death in 1569, the manuscript was printed by Castagno’s son Giovanni Paolo and had many

55 editions from 1572 to 1692 [12]. The 1572 edition of the book, published under orders by Alfonso
56 Estense Tassoni, Judge of *Savi* (wise men), contained the rules for using the *Composito* and also the
57 key sanitary rules to be practiced in the case of an outbreak. The rules contained in the *Reggimento*
58 worked so well that all cases of plague ceased since 1576 in Ferrara and they were all enclosed in
59 public proclaims and obligatory sanitary rules, even after the death of the author [13-15].

60 After the government changed from the House of Este to the papal Legation, about 32000 citizens
61 remained in Ferrara in 1601 [16]. In 1629 a new plague outbreak threatened Northern Italy [5].
62 According to the Report [17] in early November 1629 letters were brought from Venice to the health
63 officers in Ferrara reporting that plague was spreading near Milan because of the invasion of
64 Alemanni troops. The news was reported to the Pope's Legate, Cardinal Giulio Cesare Sacchetti, who
65 planned measures against the epidemics. It is known that from 1629 to 1631 the plague ravaged many
66 northern and central Italian cities, among which were Turin and Alessandria in Piedmont, Milan,
67 Mantua, Cremona, Bergamo and Brescia in Lombardy, Venice, Vicenza, Verona, Padua and Treviso
68 in Veneto, Parma, Piacenza, Bologna, Modena in Emilia-Romagna and Florence, Pistoia and Lucca
69 in Tuscany. Some locations near the legation of Ferrara, such as Abbadia nel Polesine (today Badia
70 Polesine), Imola and Budrio, were also hit (Fig. 2) [5]. In Northern Italy, only Ferrara had not been
71 affected by plague for years, due to its unique public rules.

72

73 2. Bibliographic methods

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

79 For the historical part, books, reports, manuscripts and other documents, spanning several years, were
80 consulted at the Biblioteca Comunale Ariostea (Municipal Library "Ariostea"), at the academic
81 libraries of the University of Ferrara, at the Archivio storico comunale (Historical Archives of the
82 Municipality) and at the Archivio di Stato (State Archives), all in Ferrara (Italy).

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

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

90 - “*Memorie di quanto s’è fatto per preservazione dalla Peste a Ferrara [...] ne gli Anni 1629, 1630,*
91 *1631*” (Report about what has been done to protect Ferrara from the plague [...] in the years 1629,
92 1630, 1631), henceforth “*Memorie*” [17]. This document contains the report and all public
93 announcements made in Ferrara from 1629 to 1631;

94 - “*Ordini e auuertimenti ne’ sospetti di peste, 1623*” (Orders and warnings about suspects of plague)
95 [18], henceforth “*Ordini*”.

96 - “*Reggimento contra peste*” (**Regimen** against plague), henceforth *Reggimento* written by Pietro
97 Castagno, a Spanish physician summoned in Ferrara to fight plague. The book was originally a
98 manuscript, later published in several editions since the 16th century [13-15].

99 - “*Tractato contra la peste*” (Treatise against plague) henceforth *Tractato*, written by Giovanni
100 Manardi (“Manardo”), physician and professor at the University of Ferrara since 1482 [19].

101 - “*Annali delle epidemie occorse in Italia dalle prime memorie fino al 1850, Parte Terza dall’anno*
102 *1601 al 1700*” (Annals of the epidemics which occurred in Italy from the first record up to 1850,
103 Third Part from the year 1601 to 1700), written by Alfonso Corradi, physician and professor at the
104 University of Pavia [5].

105

106 **3. Results and Discussion**

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

114

115 **3.1 Improvements in city construction**

116 Construction improvements along the centuries contributed to the successful prevention of plague in
117 Ferrara. Ferrara is known worldwide for its advanced urban planning (“Erculean Addition”), the first
118 one in the Renaissance, commissioned in 1492 by Ercole I d’Este to the architect Biagio Rossetti
119 [20]. However, since 1375 the city roads had been paved with firestones under the authority of
120 Niccolò II of Este and the first sewer system was built in 1425 [21]. The urbanistic improvements
121 provided better hygiene conditions for everyday life in the city and an easier way to identify and
122 dispose of live and dead carriers of the plague.

123

124 **3.2 Surveillance and control of people and traded goods**

125 According to *Ordini*, the city maintained a state of continuous alert about plague, with a permanent
126 surveillance team, the *Congregazione della Sanità* (“Congregation for Health”), composed of
127 authorities, noblemen, physicians and the apothecary of the Hospital [18].

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

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

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

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

160 Problems occurred at the state borders. In the small town of Bondeno, there were cases of plague due
161 to illiteracy of controllers [17]. The city of Cento, near Ferrara, was severely affected by the plague,
162 counting about 6000 deaths including five doctors who attended sick people in the lazaret. In the city
163 of Lugo, near Ravenna, the Governor failed to report certified cases of plague, thus the city was
164 ravaged with about 6000 deaths, including the Governor himself [5,17] (Fig. 1). According to
165 *Memorie*, economy was carefully supervised and money was not wasted. From November 1629 to
166 June 1631, a very high amount of money (50000 *scudi*) was spent on preventative health measures
167 [17].

168

169 3.3 Management of suspected cases

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

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

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

189

190 3.4 Hygiene rules

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

193 Concerning public hygiene, great attention was paid to the cleanliness of the city. First of all, dogs,
194 cats, chickens and pigs were identified as directly involved in the transmission of plague because they
195 were considered “filthy” (“*immondi*”). It was prohibited to raise animals such as pigs (*Bando 92, 27*

196 *marzo Nuove provvigioni, & ordini per tener netta la città; Bando 58 13 luglio Proibizione di tener*
197 *Porci, & altri animali immondi nelle Città*) [17], or other animals causing excessive dirt, such as
198 silkworms (*Bando 39, 8 giugno 1630, Sopra le Caldarane per i loro vermi, che cauano dalla seta;*
199 *Bando 98, 12 maggio 1630, Sopra i letti de Cauallieri, e vermi, che si cauano dalla seta*) [17]. It was
200 mandatory to spread large amounts of *calcina* (lime) on materials suspected to be contaminated,
201 burning (without touching them) the rags found in streets and burying carcasses of dead dogs, cats
202 and chicken [17]. Another ordinance raised attention on uncontrolled stray dogs (*Bando 53, 6 luglio*
203 *1630, Sopra l'andare i Cani sciolti*) [17].

204 In the first printed edition of the *Reggimento*, published in 1572, it was stated that materials that had
205 been in contact with sick people had to be burned to prevent contact by dogs or cats, which could
206 carry the plague inside healthy homes [14]. Concerning the way of transmission of plague by the rat
207 flea, *X. cheopis*, it is interesting to notice that rats were never mentioned among “filthy” animals.
208 Nevertheless, robes for city authorities (including physicians) were made of oilcloth “*tele incerate, ò*
209 *di Sangallo*” to prevent fleas from clinging to clothes [17]. However, plague may be transmitted by
210 other flea species, for example by the human flea *P. irritans*, which may also colonize short haired
211 mammals such as pigs and the fleas of cats *Ctenocephalides felis* (Siphonaptera: Pulicidae) and dogs,
212 *C. canis* [3,22,23]. The prevention rules established in Ferrara may therefore have been effective in
213 interfering with the activity of plague vectors.

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

216 Special care was paid to everyday hygiene rules and cleanliness in houses. In order to *smorbare le*
217 *case* (“sanitize houses”), all worthless furnishing had to be burned, throwing away all dirty or cracked
218 items and making a bright fire in the middle of the house. Perfumes had to be spread in the house for
219 fifteen days, valuable objects had to be washed and slightly heated, and money had to be warmed in
220 a fire. **Meanwhile, wool, leather clothes and lining had to be hanged up in the sun, beaten with a stick**

221 **in the evening, dried near a fire and perfumed, to make them clean and tidy** [18]. When clothes and
222 linings are exposed to the sun and beaten with a stick, it is likely that adult fleas are expelled. It is
223 known that larvae exposed to direct sunlight quickly die, being sensitive to heat and dehydration [26].
224 Probably the act of warming clothes near a fire is another effective way to get rid of immature fleas.
225 The effects of temperature and humidity on developmental stages of two flea species, *Synopsyllus*
226 *fonquerniei* (Siphonaptera: Pulicidae) and *X. cheopis*, responsible for transmission of plague, have
227 been confirmed: high temperature and low humidity have a negative effect on development [27], so
228 the rule of avoiding humidity in houses and warming people and clothing to a fire could have been
229 effective. Linen clothes had to be washed with special herbs (*Lauro, Menta & Artemisia*, probably
230 laurel, mint and sagebrush) in *liscivo* (lye), and once dry they had to be perfumed [13]. Laurel (*Laurus*
231 *nobilis*) and several species of the genera *Artemisia* and *Mentha* have been traditionally used in

232 laundry for their insecticidal/repellent properties [28,29] (Table 1). Literature data show that 1,8-
233 cineole, thujone and camphor are the major components in many essential oils of different species of
234 the genus *Artemisia* (sagebrush). The sagebrush oil not only has antimicrobial activity, but it is also
235 an insect repellent due to the presence of sesquiterpenes [30,31].

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

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

247

248 3.5 “Remedies” and personal hygiene

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

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

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

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

271 Antibacterial activity has been reported for *mirra* (myrrh, *Commiphora myrrha*) [36], *reubarbaro*
272 (*Rheum* spp.) [37], *zedoaria* (zedoary, *Curcuma zedoaria*) [38], *croco* (*Crocus sativus*) [39] and
273 *aristologra* (*Aristolochia* spp.) [40]. Repellent activity against insects has been reported for zedoary
274 [41,42]. Crocin and safranal are two important bioactive components in *C. sativus*. Some semi-
275 synthetic derivatives of safranal were tested to establish which modifications of chemical structure
276 could improve the biological activity [39] (Table 1). As far as we may presume about the components,
277 a two-action formula would have resulted, active on both the bacterium and the vector.

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

282 Acetic acid and vinegar have been recently reconsidered for antibacterial activity: they have been
283 proved effective as tuberculocidal agent and active against food-borne bacterial pathogens, including
284 *Escherichia coli* and *Salmonella enterica* (Enterobacteriales: Enterobacteriaceae) [43-46]. Acetic
285 acid with antimicrobial activity may represent an alternative to common local antiseptics. In Ferrara
286 vinegar was used undiluted to impregnate sponges to be kept in front of the mouth, for hand washing,
287 for hand ablutions, as disinfectant for unclean objects such as money and in anti-plague mixtures.

288 The traditional habit of washing hands with vinegar, or throw citrus peels on stoves or fireplaces, has
289 been practiced until recent times. Antiseptic properties are traditionally attributed to vinegar, citrus,
290 gentian and rue, and the common practice of wetting hands, face and body could have built a sort of
291 barrier against the plague bacterium and the vector.

292 Personal hygiene at that time in Ferrara was unusually mandatory and performed by ablutions, daily
293 linen changes and diffusion of scents in rooms. Antiseptic effects were achieved by wetting hands
294 and face with vinegar, or by brushing a sponge all over the body. Vinegar was used alone or as *aceto*
295 *rosato* (rose vinegar), in a mixture with *acqua rosa*, *e vin bianco* (rose water and white wine) added
296 with *Carlina*, *Genziana*, *radice di Ruta Capraria*, *detta Giarga*, *Scorza di Cedro*, *Gedoaria* [13]. The
297 mixture was recommended for hygiene of hands and body, but also for oral administration through a
298 few drops. The genus name *Carlina* honors the Holy Roman Emperor Charlemagne or, according to
299 other authors, Charles V. The emperors were said to have used the plant against the plague for their
300 soldiers. Antimicrobial properties have been reported for *Carlina* (*Carlinae radix*) [47], *genziana*
301 (*Gentiana lutea*) [48], *ruta capraria* (goat’s rue, *Galega officinalis*) [49] and *scorza di cedro* (cedar,
302 *Citrus medica*) [50]. Moreover, significant antimicrobial effects have been reported for essential oil
303 and decoction of *G. officinalis*, supporting its use in ethnomedicine [49].

304 Mangiferin, isogentisin and gentiopicrin were isolated from methanolic extracts of flowers and leaves
305 of *G. lutea*. The synergistic activity of these compounds may be responsible for the positive
306 antimicrobial effects reported for its the extract [48]. *Gedoaria* (zedoary) combines repellent efficacy
307 [41] with antimicrobial activity [38] (Table 1).

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

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

314 The bag to be used in winter (*Quella del verno*) contained *storace, iride, garyophili, mace, nuce*
315 *muscata, cinnamomo, zafrano, ambra, muschio*. *Garyophili* (clove oil from *Syzygium aromaticum*,
316 syn. *Eugenia caryophyllata*) has been reported as acaricidal on house dust mites by direct contact
317 [51]. Clove oil in its major components (eugenol and β -caryophyllene) has repellent activity also
318 towards body lice (*Pediculus humanus*, Anoplura: Pediculidae) [52]. *Nuce muscata* and *mace*
319 (essential oils of seeds, nutmeg, and aril of *Myristica fragrans*) have recently shown adulticidal
320 activity against *Aedes aegypti* [53]. Myristicin and trimyristin, components of *M. fragrans*, have
321 shown antibacterial activity [54]. Ethyl acetate and ethanol extracts of *M. fragrans* have been
322 successfully tested as new natural agents for oral care products against cariogenic and
323 periodontopathic bacteria [55].

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

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

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

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

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

340 The components of Manardi's *sacheti* were the basis of the corresponding scent-ball formulations,
341 *Balle del Verno e dala Estate*. The scent-ball was made of perforated cypress or ash wood which
342 contained a sponge soaked in a mixture of the cited substances and *aqua Rosata & Malvasia* (rose
343 water & Malmsey wine) & *mezza parte di aceto* ("half amount of vinegar). It was held in the hand
344 for smelling, but it could also be shaken on the hands, rubbing the liquid on the face. These scent-
345 balls could have exerted some antibacterial activity towards airways and possibly block the diffusion
346 of infected aerosol. The same activity was probably exerted by vinegar used to impregnate sponges
347 to be kept in front of the airways.

348

349 3.6 Studies on plague epidemics

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

352 General preventative measures against epidemics, such as health magistrates and quarantine
353 procedures, were commonly attempted along the centuries [24,63,64,66]. As previously mentioned,
354 Ferrara succeeded in controlling plague since 1576 [12,14]. An interesting attempt to control the
355 plague outbreak of 1582-1583 through sanitary rules was that by Protomedicus Quinto Tiberio
356 Angelerio in Alghero (Sardinia), which had about 4000 inhabitants at that time [6]. However,
357 Angelerio's rules had only limited success because of inactivity from authorities and hostility from
358 population about a required commercial block [6]. The relevant difference between the case of
359 Alghero and that of Ferrara is the fact that the preventative measures established in Ferrara in 1629-
360 1630 were able to protect not only a city of about 32000 inhabitants, but also the entire territory of
361 the papal legation, including all towns and villages inside it, and the measures were effective while
362 the entire Northern Italy was the battlefield for the war of Mantuan Succession.

363

364 6. Conclusions

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

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

375 The empirical and cooperative “integrated disease management employed in Ferrara during the
376 Italian Plague (1629-1631) is similar to the rules of prevention, surveillance and control
377 recommended by World Health Organization (WHO) [1] to manage plague outbreaks (Table 2).
378 In order to protect the city of Ferrara and its surroundings from the rampaging infection, the key
379 factors were the awareness of the role of dogs, cats, chicken and pigs in the transmission of plague
380 and the development of “rimedi” (remedies), whose components have been recently shown to have
381 antibacterial, insecticidal and insect repellent activity (Table 1).
382 This study represents a base for further investigations on components of these remedies that exhibit
383 some insecticide and repellent activity towards vectors of plague and other diseases, within a
384 dedicated project of the University of Ferrara. As reported by WHO [1] from 2010 to 2015 there were
385 3248 cases of plague reported worldwide, including 584 deaths. Nowadays, plague is easily treated
386 with antibiotics and the use of standard precautions to prevent acquiring infection. Historical remedies
387 practiced in Ferrara during the Italian plague to protect the city could surprisingly represent an
388 innovative research field aimed to prevention of dangerous emerging diseases.

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395

396 **Conflict of interest**

397 The authors declare that they have no conflict of interest.

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601 **Figure captions**

602 **Fig. 1.** Detail of a geographical map by Giovanni Antonio Magini [69] showing the papal Legation
603 of Ferrara and the nearby territories. The yellow line shows the boundaries of the Legation and the
604 small flags the locations struck by the 1629 plague. 1, Ponte di Lago Scuro; 2, Bondeno; 3, Cento;
605 4, Lugo.

606
607 **Fig. 2.** Detail of a map of Italy by G. A. Magini showing Northern Italy and part of Central Italy
608 [70]. The map reports the main Italian cities struck by plague from 1629 to 1631 (red flags). The
609 green flag indicates the city of Ferrara which was spared by the epidemics.

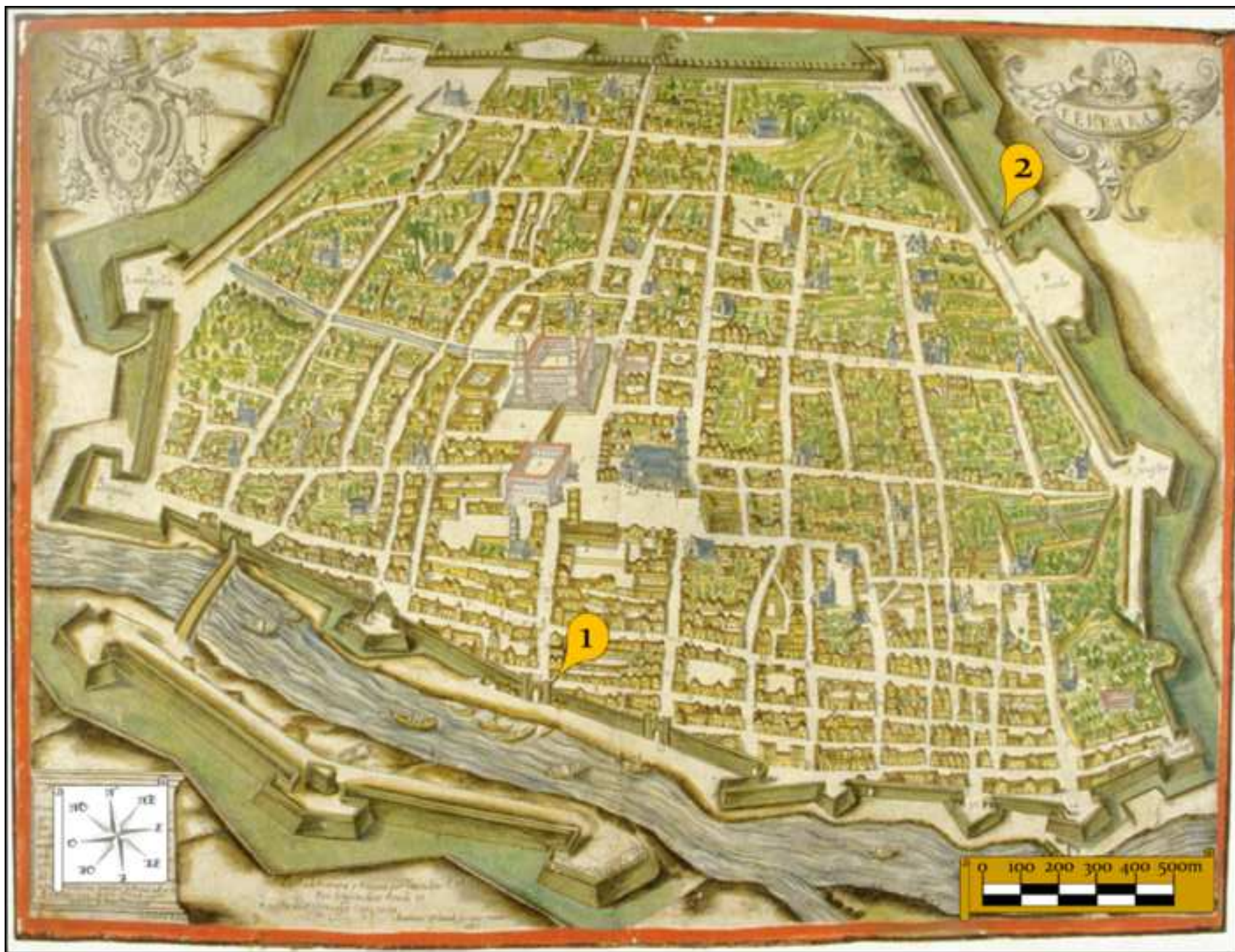
610
611 **Fig. 3.** City of Ferrara [71] at the beginning of XVII century. The map of the city indicates the only
612 two gates which were kept open upon news of plague outbreaks: 1, Porta San Paolo; 2, Porta San
613 Giovanni Battista.

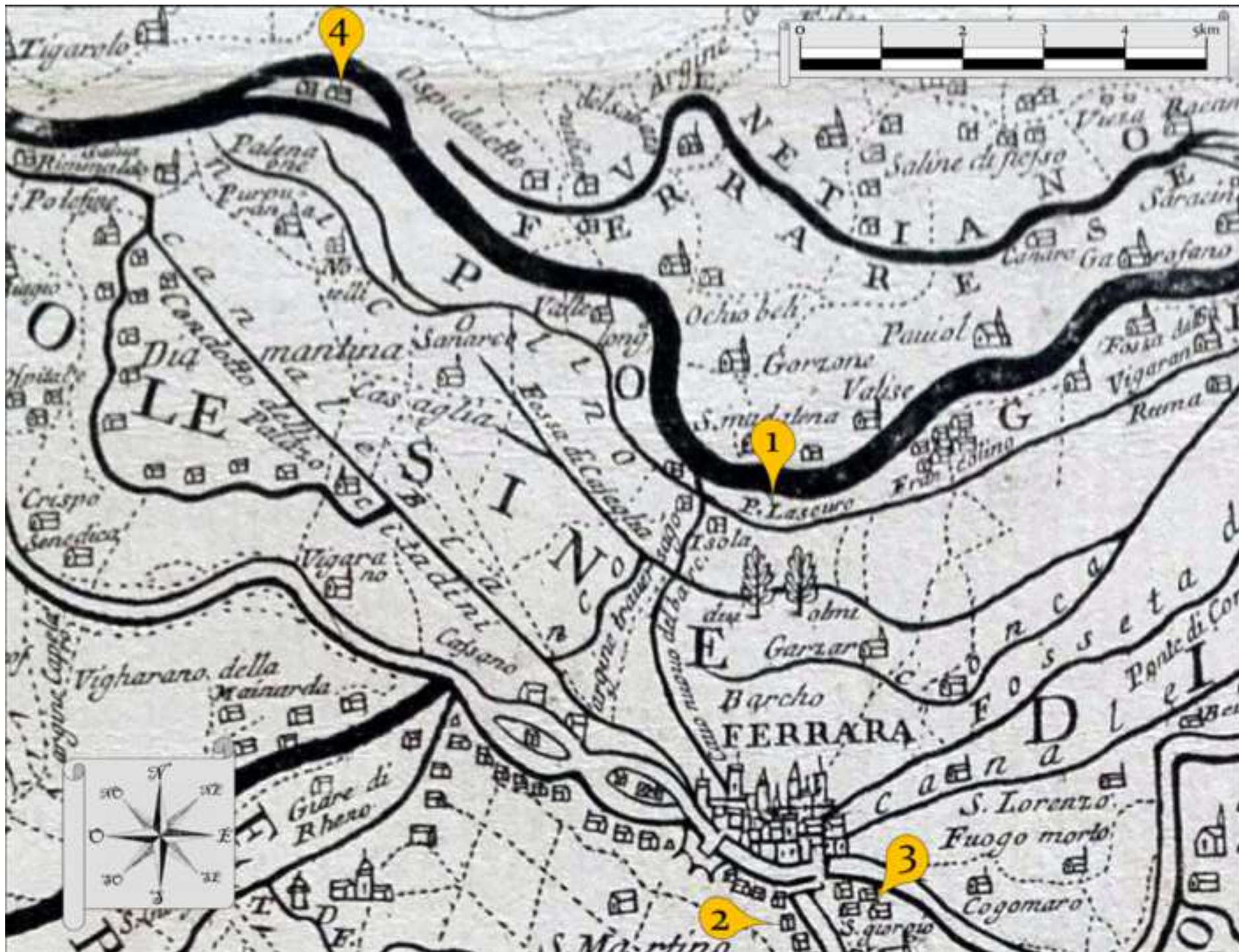
614
615 **Fig. 4.** City of Ferrara and its surroundings [72] at the beginning of XVII century. The map
616 indicates the positions of the lazarets, of which two were operative (1, Ponte di Lago Scuro; 2,
617 Borgo San Luca), two supplementary (3, monastery of the Olivetans in San Giorgio and ship
618 dockyards) and one planned (4, island of Bonello).

619











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Table

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