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Bedbugs, *Cimex* spp.: their current world resurgence and healthcare impact

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ABSTRACT

Over the past two decades there has been a worldwide spread of blood-sucking bedbugs (Cimicidae), leading to naming them a re-emerging plague. New hosts and species have been reported and even vector-borne diseases have been associated to Cimicidae, though the latter is not fully established yet. *Cimex*, which is the most representative genus, is well-known for its parasitic capacity, worldwide distribution and for being considered by many authors as a man-spread plague. The healthcare impacts of *Cimex* invasion are being studied, but currently it is considered an alarming public health concern that has been defined by the U.S. Environmental Protection Agency as "a pest of significant public health importance". In this review, the general characteristics of *Cimex*, its morphology and its current geographical distribution are discussed not only in developed countries but also including nations from South America, Africa and Asia. Furthermore, we briefly describe the impact that Cimicidae has had on public health, and especially the medical importance of bites, focusing on the possible vector-borne diseases newly reported in the literature including wild species of cimicids.

1. Introduction

Cimicidae is an important family of ectoparasites widely known because of their extensive global distribution and particularly the healthcare impacts caused by the genus *Cimex*. The family belongs to the suborder Heteroptera, order Hemiptera, class Insecta and phylum Arthropoda. These insects are blood-sucking bugs that use a variety of mammals and birds as hosts, from which they feed off at night, being able to survive a year without feeding again[1]. Their close relationship with humans initiated in the Middle East caves, where these bugs lived with bats and were able to go on these primitive men[2]. Since then, these ectoparasites have been transported mechanically by humans, adapting and surviving under increasingly diverse environments until they finally became a global plague[3-5].

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Adaptation to new hosts and environments has allowed classification of around 100 species of Cimicidae into 6 subfamilies organized in 22 genera including human bedbugs, bat bugs and bird bugs. Specifically, the literature has reported 12 cimicids' genera exclusive for bats, nine more for birds and one genus for human bugs called *Cimex*.

Latter mentioned is of special importance because it contains two important species, the cosmopolitan *Cimex lectularius* (*C. lectularius*), and the tropical *Cimex hemipterus* (*C. hemipterus*) (Figure 1), which only feed on humans (rarely on other hosts) and consequently have a strong biological relationship with humans[6]. It has been reported that *C. lectularius* is the most common, while *C. hemipterus* is the only one capable of adapting to the tropical weather[7]. There are many other species, such as *Leptocimex boueti*, which live in East Africa and feed off both humans and bats[2].

These two species are popularly known as "bedbugs", *C. lectularius* and *C. hemipterus*, because they are often found hidden in mattresses, under beds or directly in their resting place, in cracks and crevices on the walls, furniture or other clefts in the architecture, making them difficult to find in the daytime by common people. Cimicidae are hematophagous since the juvenile stages, thus becoming a problem for a longer period of time[1]. Many studies have described infestation rates approaching 90% in neighborhoods, towns and even whole cities, also it was found that population density and volume are directly associated to these high percentages[2]. According to popular belief good sanitation is a key to minimize bed bug impacts, however there is evidence which suggests that the level of sanitation is not a good indicator of the presence of bedbugs[2,5].

Figure 1. Habitus of *C. lectularius* (left) and *C. hemipterus* (right).

There are other species out of the genus *Cimex*, that invade human settlements due to the proximity of their hosts' dwellings, either nests for birds or caves or under roof for bats. The extensive spread of the human-associated cimicids and the ability of wild species to transmit infectious diseases to birds and bats raise the question of the potential vector role of bedbugs. In the present paper we address these questions using recent data in order to present the current global distribution of *Cimex*, the possible vector properties of the re-emerging plague and also the medical impact that it has generated.

2. Search strategy and selection criteria

In this review, data were identified by rigorous searches of major bibliographic databases, *i.e.,* MEDLINE, PubMed, EMBASE, Scopus, Google Scholar, Ovid, Lilacs, ScienceDirect, Current Contents, and the World Health Organization (WHO) database. Our search terms were "Cimicidae", "*Cimex*", "bedbugs" in combination with "re-emergent plague" or "public health" or "infectious diseases" or "communicable diseases", "emerging" or "vector-borne diseases". We focused our objective on experimental studies, original articles, case reports, systematic and non-systematic reviews, community-based studies, and other entomological findings. Selection criteria included a judgment about the relevance to describe *Cimex* as a public health concern and for the well informed and updated status of *Cimex*. We cited review articles where they provided comprehensive overviews. Abstracts and reports from meetings were included only when they related directly to previously published work. We mainly selected articles published in the past 30 years, but did not exclude important older articles. Hand search of the articles on medical importance of Cimicidae was conducted without limits of language, if they were not available virtually the physical copies of the journals were sought. Initial searches were performed in July 2013, with updates in December 2013, February 2014 and September 2014.

The state of the art and the current epidemiological status of *Cimex* spp. in each country (according to the continent) analyzed were supplemented by data information of published reports and in some cases from personal communication, via e-mails, made with researchers and entomology experts. Current articles of health education material and entomology communication were analyzed with the purpose of finding more information about the family Cimicidae as vectors and to provide an updated illustration of the world distribution of the re-emergent plague, respectively. This systematic search generated a high number of articles, which were further shortlisted for inclusion in the review. Full texts of all relevant articles and the information received from experts were read and analyzed, and available evidences and main findings were summarized.

We thus have resorted to an extensive search of data not only from multiple databases but also from a lot of authors which have had experience with cimicid' plagues. Finally, many of the analyses for this Review come from the global perception reflected in medical and entomological literature. Our compiled data generate what we believe to be the most possible robust discussion.

3. From darkness to light

History of Cimicidae species is not well documented, although their interaction with humans is thought to have begun when Neanderthals or Cro-Magnons lived in caves invaded with bats and bedbugs. After adaptation to human, bedbugs were transported to settlements where the world civilizations would then arise[1,2].

Bedbugs were first considered a relevant plague between the early 20th century and the end of the Second World War, when developed countries launched different insect eradication campaigns of bedbugs using dichlorodiphenyltrichloroethane (DDT) and other chemicals. These efforts were able to significantly decrease the number of infestations[4,8]. Despite the common use of insecticides and the popular belief of their extinction, in the last two decades several pest control agencies have announced with concern the rise of re-emerging infestations resistant to older insecticides. This alarming situation has been experienced by populations of developed countries, such as Canada, the United States of America (USA), Great Britain and Australia, among others (Table 1)[5,8]. Some hypotheses blame the resurgence on the following: (1) the elevated migration rates that favor passive dispersal, (2) changes in pest management practices due to the strict regulation of the marketing of pesticides, (3) the development of resistance to insecticides and (4) the profound gaps in knowledge about Cimicidae[2,9].

4. Morphology and biology main features of Cimicidae

Members of the Cimicidae show some common characteristics with other hematophagous arthropods and have some unique ones in this family. They are biting-sucking insects, which possess stylet bundles to reach directly into blood vessels; *i.e.*, they are solenophagous, same as mosquitoes and triatomines. Their life cycle is paurometabolous, meaning that the young ones are similar to adults and that all life stages are hematophagous. Their parasitic life has simplified themselves: no wings, no ocelli, and small number of sensors on the antennae. The traumatic insemination is uncommon and is shared with few other arthropods[10]. Traumatic insemination is a way of penetration for pathogens into the female body and may cause their death or reinforce their immunity. This may be an explanation of pathogen control by females. Another interesting feature is the bacteriolytic activity of the cimicid bugs' sperm[11].

The scent apparatus is well developed and plays an important role in relations between individuals and aggregation behavior[12,13]. Cimicidae possess mycetomes, particular organs dedicated to the endosymbionts[1], which are microorganisms essential for the life of these insects and which reveal an ancient adaptation to hematophagy.

Table 1

Countries with alarming case reports and other studies where *Cimex* spp. have been considered a public health concern since the last decades.

Continent	Country	*Cimex* species*	References
Asia	Bangladesh	*C. hemipterus*	[31]
	Cambodia	*C. hemipterus*	a
	China	*C. lectularius*, *C. hemipterus*	[28]
	India	*C. hemipterus* (south), *C. hemipterus* (north)	[36,37]
	Indonesia	*C. hemipterus*	a
	Iran	*C. lectularius*	[38]
	Israel	*C. lectularius*, *C. hemipterus*	[33,34]
	Japan	*C. lectularius*	a
	Laos	*C. hemipterus*	a
	Malaysia	*C. hemipterus*	[30]
	Myammar	*C. hemipterus*	a
	Pakistan	*C. hemipterus*, *C. hemipterus*	[37]
	Papua New Guinea	*Cimex* sp.	[103]
	Philippines	*C. hemipterus*	a
	Singapore	*C. lectularius*, *C. hemipterus*	[30]
	South Korea	*C. lectularius*	[32]
	Sri Lanka	*C. hemipterus*	[29]
	Thailand	*C. hemipterus*, *C. lectularius* (north)	[27,35,39]
Australia		*C. lectularius*, *C. hemipterus*	[4]
The Americas	Argentina	*C. lectularius*	[50]
	Brazil	*C. lectularius*, *C. hemipterus*	[49]
	Canada	*C. lectularius*	[5]
	Chile	*C. lectularius*	[50]
	United States of America	*C. lectularius*	[47,48]
	Peru	*C. lectularius*	[65]
	Venezuela	*C. lectularius*, *C. hemipterus*	[51]
Africa	Nigeria	*C. lectularius*, *C. hemipterus*	[40,41]
	Réunion	*C. hemipterus*	c
	Rwanda	*C. hemipterus*	[43]
	Senegal	*C. hemipterus*	d
	Sierra Leone	*C. hemipterus*, *C. lectularius*	[44]
	South Africa	*C. hemipterus*, *C. lectularius*	[45,46]
	Tanzania	*C. hemipterus*, *C. lectularius*	[42]
	The Gambie	*C. hemipterus*	d
Europe	Austria	*C. lectularius*	[17]
	Czech Republic	*C. lectularius*	[17]
	Denmark	*C. lectularius*	[19]
	France	*C. lectularius*	[21,58]
	Germany	*C. lectularius*	[20]
	Italy	*C. lectularius*	[22,23]
	Norway	*C. lectularius*	[24]
	Poland	*C. lectularius*	[17]
	Russia	*C. lectularius*	[25]
	Slovakia	*C. lectularius*	[17]
	Spain	*C. lectularius*	[26]
	Sweden	*C. lectularius*	[17]
	Switzerland	*C. lectularius*	[17]
	United Kingdom	*C. lectularius* > *Cimex pipistrelli*	[8,18]

*: *Cimex* species as re-emergent plagues reported with a public health significance and per country. a: Chow-Yang Lee, Universiti Sains Malaysia, Penang, Malaysia (personal communication); c: Jean-Michel Bérenger's data, Aix Marseille Université, Marseille, France (personal communication); d: Oleg Mediannikov-IRD, Dakar, Senegal (personal communication).

5. Current distribution of *Cimex* spp.

Authors have idealized different methodologies for qualify and quantify the world resurgence of bed bug[1,14-16]. The first proximity was given by Usinger's monograph in which there is a published distribution map of the two species of bedbugs, *C. lectularius* settled down in nearctic and palearctic areas, and *C. hemipterus* located in the tropical areas[1]. Actually regarding the second resurgence, many papers make reference only to the problem in industrial countries such as the USA, Canada, Australia and some European countries. The situation in Africa, South Asia and South and Central America is poorly documented.

In Figure 2, we have reported the countries where *Cimex* spp. are considered a public health concern since last decades, by means of data information from papers, local journal, the web and from entomologist colleagues residing in these countries where they are very aware of the problem magnitude. For some countries, such as Panama and Papua New Guinea, for which no recent data is available, we have taken old papers (Panama, Papua New Guinea). The map shows an evident increase of bedbugs in the aforementioned places, especially with the species *C. hemipterus*, but sympatric exist with *C. lectularius* in several countries. In South America, there are few reports of *Cimex* spp. infestations and hence it has not been considered an alarming plague over the past decade. Latin American countries, including Colombia, Venezuela, Panama, Ecuador, Peru, Chile and Argentina have not had the same experiences than the USA, European or Asian countries.

In Europe, *C. lectularius* is implicated in the most of countries in this continent[17-26]. The number of infestations has achieved alarming rates and there is a similar situation in the USA, with complicated plagues and more quotidian critical reports of infestations[14].

In Southeast Asia, *C. hemipterus* seems to be the main species implicated in infestations, and in other parts of Asia (outside Southeast Asia) such as China, Japan and Korea, *C. lectularius* is more common[27-39]. For India, both are common species and have similar proportion, *C. hemipterus* in the south, while *C. lectularius* in Northern India[36,37]. In Africa, there are several related publications but we consider that the real number of infestations (without reports) might be even more due to the low rates of entomological and epidemiological surveillance in this continent[40-46]. Also, Latin America shares the same context about the lack of surveillance on this topic[5,47-51]. In these countries, bedbugs are just considered a nuisance and thus relatively minor issues are not reported on. Several papers were found for countries and summarized in Table 1.

Despite the great number of infestations in France, we have investigated the Antilles (Martinique) where just one case in 2012 has been reported from people returning from Africa with *C. hemipterus* and one case in 2013 in French Guiana from people spending one night in a French airport hotel (Figure 2). On the other hand, the problem increased in Reunion Island with *C. hemipterus* according to data based on pest controller intervention and local journal. In Israel, *C. hemipterus* is a local health problem in this country, though only *C. lectularius* is well established and spread in this country.

Despite the scarce entomological literature and reports of *Cimex* in developing countries, different authors affirm that bedbugs are a big problem in the developing world, where people have to deal with numerous vector-borne disease section, infectious diseases, as

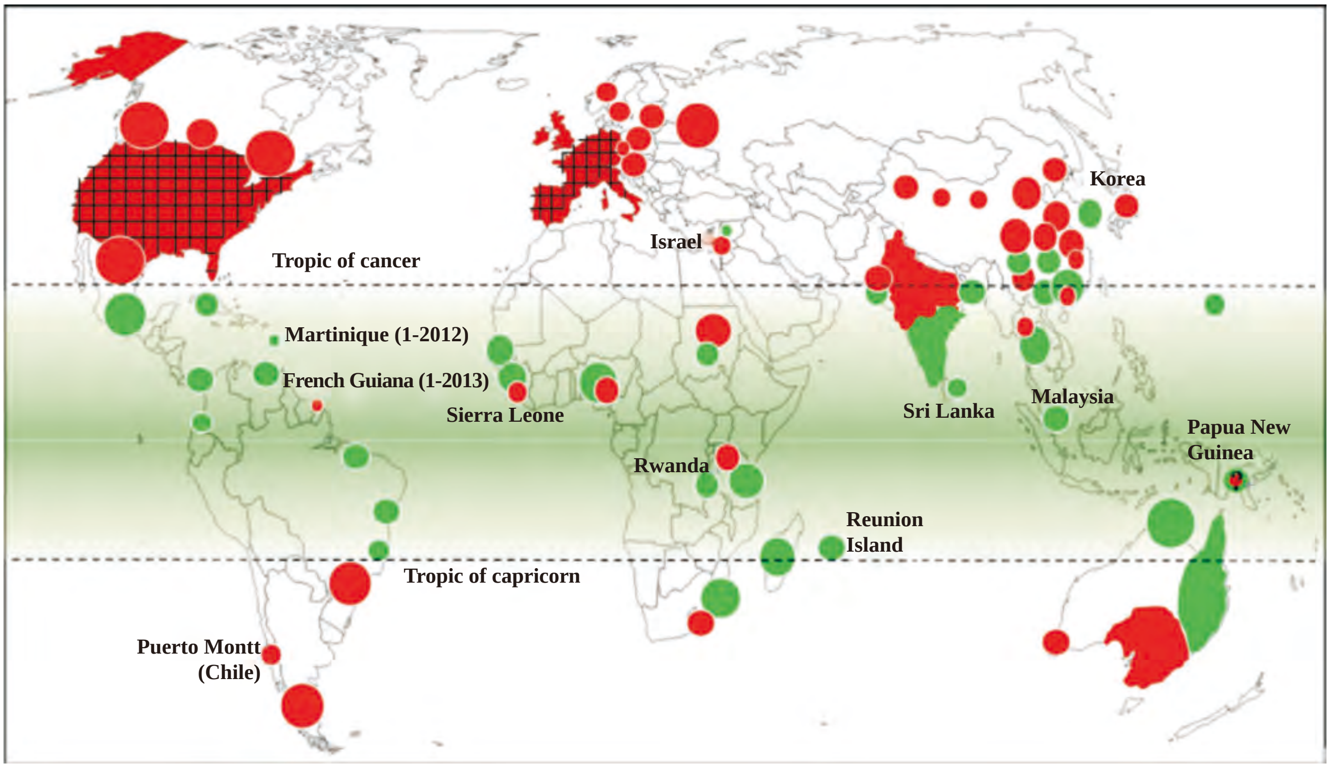

Figure 2. Updated world map of bedbug infestations.

Red circles represent reported infestations of *C. lectularius*, green circles represent reported infestations of *C. hemipterus*, red-green circle plus question mark (?) represent infestations with unspecified species (*e.g.* Papua New Guinea), and color dark red plus black lines represents places where *C. lectularius* has caused critical economic and health impacts. Superior line spacing represents the tropic of cancer and the inferior line spacing represents the tropic of capricorn. Between the tropics of cancer (superior line spacing) and capricorn (inferior line spacing), the predominant specie is *C. hemipterus* (there are few exceptions), while in the rest of the world the predominant is *C. lectularius*.

well as malnourishment. Recently, Potter and colleagues confirm the global pandemic of bedbugs by means of online surveys developed for company respondents from 43 countries, resulting high rates of affirmative answers in USA (95% of 521 respondents), Canada (98% of 64 respondents), Europe (92% of 113 respondents), Africa/Middle East (90% of 10 respondents) and Asia (73%). Latin America had the lowest rate compared with overall continents (59% of 208 respondents)[15].

There are other interactive forms created with the purpose of quantify the distribution of "bedbugs" like the web platform BedBugs.NET©[16]. Despite the maps focus on reports made by common people it is not a liable method for study the global resurgence.

6. Medical importance and public health significance

6.1. Clinical effects of bedbugs

The physical, mental and economic impact of *Cimex* spp. lies on its bite[1,2]. Consequences of bedbug bites include (1) direct consequences: allergic reaction (due to saliva), pathogens transmission (unclear yet), psychological effects, anemia (iron deficiency); (2) indirect consequences: acute illnesses (associated with toxicity of bedbugs' insecticides).

A lot of people in the world suffer severe allergic reactions to the salivary components, which may even trigger clinical symptoms of anaphylaxis[52-55]. The dermatological effects that have been documented are dermatitis, impetigo, ecthyma, lymphangitis and folliculitis, as well as stinging reaction caused by the bite[9,56-58], and in case of chronic infestation it could cause disseminated bullous eruption with systemic reaction, lethargy, diarrhea and discomfort[59]. In addition, mental alterations have been reported linked to household infestations, and among the most common effects are anxiety and insomnia even after the plague has been exterminated.

Bedbug bites usually do not cause pain due to the chemicals released through the proboscis along with saliva which temporally anesthetize a small region[2]. However, after a few hours the host feels pain related to immunological responses. The lesion generated is a sore of approximately 1.5 cm in diameter and cutaneous eruptions may be produced. In the 21st century, there have been some variations of the dermatological manifestations. One of these curious changes is the otitis or the ear irritation due to engorged nymph forms of *C. lectularius* found in the ear canal[60]. Other examples are several skin syndromes, including severe bullous reactions that resemble the Churg-Strauss syndrome[61]. These diverse reactions are a consequence of anti-coagulating and vaso-dilating proteins present in the saliva. Given that the clinical response depends on the host's sensibility, only in some cases a second bite is even required to produce the reactions mentioned. Other systemic symptoms which may occur are fever, anemia, and asthmatic crisis[54,55,62]. We noticed during our investigations that some people exposed to many bites have no marks on their skin; immunization against bedbugs saliva seems to exist. Interestingly in the last year, pediatric patients have experienced particular immunological reactions along with erythema, edema and subsequent papules on one or both upper eyelids[63]. Recently, the severe reactions observed in this type of population has been related with the IgE-mediated hypersensitivity to nitrophorin protein (cNP, a known allergen component of the salivary

C. lectularius) when they are being bitten by bedbugs[64]. However, actually in pediatrics there are difficulties to determine the culprit insect involved in cases of arthropods assaults, and the diagnosis is considered a challenge due to the variability of the clinical appearance[63]. Treatment of complications consists in topical steroids for control of the inflammation, topical antibiotics and antiseptics to prevent secondary infections and antihistamines to avoid serious sensibility reactions and other allergies.

Currently, the transmission of infectious agents is a discussed topic because several authors have demonstrated the important role of bedbugs as disease vectors under special laboratory conditions[65]. As a counterpoint, some studies refer to salivary components that could inhibit the growth of certain bacteria such as *Staphylococcus albus*[66], and prevent germination of fungal spores such as *Curvularia lunata* and *Fusarium oxysporum*[67]. In the next section of this review we resume this topic.

Severe anemia is described in literature, generally with seniors or people with poor health[62,68,69]. Usinger described his experience when he reared bedbugs on himself during seven years; hemoglobin concentration was initially 14.5 g/dL and it fell to 11.5 g/dL after some months. It is thought that the problem with the repeated blood meals is the decrease of iron level in the blood.

In the USA there has been a strong concern about toxicity rates caused by the excessive use of insecticides or use of insecticides contrary to label directions[70]. As we have mentioned, bedbugs infestations are treated with insecticides which unfortunately it have not shown the same effects compared with the first emerging plague, such as the case of DDT (in World War II). Usually, people use insecticides with alarming doses and in not recommended places with the false mind that higher doses application will eradicate bedbugs from their homes. Between 2003 and 2010, there were seven states in the USA, where a total of 111 illnesses associated with bedbugs-related insecticide use were identified. From the report of the Centers for Diseases Control and Prevention[70], it is important to denote that the number of cases of acute illnesses had an exponential increment year by year during the period evaluated (2003 to 2010), and due to that we consider it could be another serious problem related with bedbugs in the future. During the indicated period, 81% (90 out of 111 cases) were low severity, 18% (20 out of 111 cases) were moderate severity, and only one fatality occurred. Curiously, New York City had the largest percentage of cases 58% (68 out of 111 cases), probably due to the high density population.

About the economic impact of these bugs, the exact values are unknown but there has been a huge investment in infestation control on domestic premises and losses of wages of the bedbugs' victims. Approximately, 50% of the total quantity of bedbugs infestations around the world occurs in developed countries[9].

6.2. Infectious diseases transmission and vector-borne diseases

The possible ways of contamination are: (1) salivary gland: injection of pathogen directly in blood vessels; possible for arboviruses with wild species of Cimicidae. Goddard *et al*. found *Rickettsia parkeri* (*R. parkeri*) in salivary glands of *C. lectularius* after an infected blood meal in laboratory[71]. (2) Feces, which can contain the living pathogen[65].They are numerous and emitted around the resting place and so, into the human environment (Figure 3).

Crushing of the insect which are fragile when engorged (Figure 4) and their contact with a bite hole or a mucous membrane. Contamination could happen with *Bartonella quintana* (*B. quintana*) if future research proved the bacteria is alive in the bedbug gut (as the same for body lice).

Figure 3. Feces of bedbugs on a house wall.

Figure 4. *Cimex* lectularius, engorged stage I.

As we mentioned above, there are no definitive reports of pathogens transmitted by Cimicidae to human so far. However, there are several studies that show the possibility of their future role in the field of vector-borne diseases and even recent reports attribute nearly 45 microbes as transmissible by *C. lectularius* but without enough evidence of diseases arising from that transmission[65,72-77]. Most of these studies have been made on wild or on laboratory colonies of Cimicidae and have artificially found temporary transmission of a variety of infectious agents (Table 2). In the Figure 5, we show the global distribution of the possible transmissible microorganisms in Cimicidae which have been recently found or missing in previous publications[72]. This review postulate 20 more pathogens (Table 2) updated or even missed in several reviews about Cimicidae such as Delaunay and colleagues[72], and we conclude by means of updated data information that so far there are in total approximately 65 microorganisms associated to the possible vector capacity of Cimicidae and even it might be higher in the next decades. The updated or missed microorganisms' list (Table 2) included 15 bacteria: *B. quintana*[43], *Bartonella* sp.[78], *Brucella abortus*[79], *R. parkeri*[71], *Enterobacter hormaechei* (*E. hormaechei*)[80], *Stenotrophomonas maltophilia* (*S. maltophilia*)[80], *Bacillus licheniformis* (*B. licheniformis*)[80], *Sarcina flava*[81], *Bacterium tegumenticola*[81], *Tsukamullera paurometabola*[81], *Burkholderia multivorans*[82], *Staphylococcus* *epidermidis* (*S. epidermidis*)[76], *Staphylococcus arlettae*[76], *Micrococcus*[76,80,81], *Kocuria kristinae* (*K. kristinae*)[76], and five viruses: Fort Morgan virus[83,84], Buggy Creek virus[85-87], Tonate virus[88], Eastern equine encephalitis virus[73], Kaeng Khoi virus[89]. Although the majority of microorganisms are nonpathogenic (Table 2), the extension of the list show the strong speculative idea of bedbugs as vectors of infectious diseases.

We were able to find in the literature some of the microorganisms confirmed in wild *Cimex*: *Candidatus Midichloria mitochondrii*[75], *Coxiella burnetii*[79], *Wolbachia* spp.[1,74,90], *Aspergillus flavus*[79], *Penicillium* spp.[79], *Scopulariopsis* spp.[79], *Brugia malayi*[79], *Wuchereria bancrofti*[79], Reovirus[79], Fort Morgan virus[83,84], Buggy Creek virus[85-87], and Kaeng Khoi virus[89]. In addition, there are other possible agents transmitted experimentally, such as *Brucella melitensis*[79], *Rickettsia rickettsii*[79], *Trypanosoma cruzi* (*T. cruzi*)[65], *S. maltophilia*[80], *E. hormaechei*[80], *Staphylococcus saprophyticus*[80], *B. licheniformis*[80], *Penicillium* spp.[80], and Hepatitis B, C and E viruses[79]. The reasonable vector-borne diseases that have not been reported yet (but there are strong speculations) are *Mycobacterium tuberculosis*[79], *Yersinia pestis*[79], *Plasmodium* spp.[79], *Trypanosoma gambiense*[79], Influenza virus[72], the Eastern equine encephalitis virus[73], and the avian paramyxovirus type 4[91]. The latter has been isolated from particular bugs (*Oeciacus hirundinis*) collected in nests in Slovakia, but the transmission is also unclear yet.

There are many other microorganisms not clarified yet and unlikely to become pathogenic because of the time duration of the microbe within the Cimicidae experimentally. Some researchers were able to keep some infectious agents alive for a short time on *Cimex* spp., as in the case of the Mexican typhus bacteria (*Rickettsia typhi*) on *C. lectularius* for 10 days. Another example is the isolation of *Borrelia hermsii* which

Table 2

Summary of 20 transmissible microorganisms updated (in total there are 65 microorganisms in total studied in Cimex, including 20 provided in this review plus other 45 provided by Delaunay et al.[72]).

Microorganim		Pathogenicity[a]	Year of the first report	Laboratory[b]	Part of the body[c]	Genus and Specie	Region, (Country)	No. Ref.
Bacteria	*Brucella abortus*	High	1947	Experimentally (survived in the bugs for 90 days)	Gut	*C. lectularius*	-	[79]
	Tsukamullera paurometabolum	High	1941	Naturally	Ovaries, mycetome	*C. lectularius*	Columbus, Ohio (USA) [Colony bedbugs]	[81]
	Bacterium tegumenticola	NS	1941	Naturally	Integument	*C. lectularius*	Columbus, Ohio (USA) [Colony bedbugs]	[81]
	Micrococcus conglomeratus	NS	1941	Naturally	Hind-intestine, whole body homogenate of the bedbug	*C. lectularius*	Columbus, Ohio (USA) [Colony bedbugs] Rifle, Colorado (USA)	[76] [80] [81]
	Sarcina flava	Middle	1941	Naturally	Triturated specimen	*C. lectularius*	Columbus, Ohio (USA) [Colony bedbugs]	[81]
	B. licheniformis	High	2005	Naturally	Male reproductive organ	*C. lectularius*	Sheffield (United Kingdom) [Colony bedbugs]	[80]
	S. maltophilia	High	2005	Naturally	Male reproductive organ	*C. lectularius*	Sheffield (United Kingdom) [Colony bedbugs]	[80]
	E. hormaechei	High	2005	Naturally	Male reproductive organ	*C. lectularius*	Sheffield (United Kingdom) [Colony bedbugs]	[80]
	Bartonella sp.	High	2005	Naturally	Entire body	*C. adjunctus*	Orangeburg, South of Carolina (USA)	[78]
	R. parkeri	High	2012	Experimentally (survived in the bugs for 14 days)	Salivary glands and entire body	*C. lectularius*	Starkville, Mississippi (USA). [Colony bedbugs]	[71]
	Staphylococcus arlattae	NS	2013	Naturally	Surface of the bedbug	*C. lectularius*	Fort Dix, New Jersey (USA). [Colony bedbug]	[76]
	S. epidermidis	NS	2013	Naturally	Whole body homogenate of the bedbug	*C. lectularius*	Fort Dix, New Jersey (USA). [Colony bedbug]	[76]
	K. kristinae	Middle	2013	Naturally	Surface of the bedbug	*C. lectularius*	Rifle, Colorado (USA)	[76]
	B. quintana	High	2013	Naturally	Whole body homogenate of the bedbug	*C. hemipterus*	Miyove & Muhanga, (Rwanda)	[43]
	Burkholderia multivorans	High	2013	Naturally	Entire body	*C. lectularius*	Raleigh, North Carolina (USA)	[82]
Virus	Fort Morgan virus	Middle	1973	Naturally		*O. vicarius*	Fort Morgan, Colorado (USA)	[83] [84] [87]
	Buggy Creek virus	NS	1980	Naturally	Egg pools (vertical transmission)	*Oeciacus vicarius*	West central Oklahoma, Southwestern Nebraska. (USA).	[104] [85] [86] [105]
	Tonate virus~Venezuelan equine encephalitis virus	High	1974-1976	Naturally	NP	*Oeciacus vicarius*	-	[79]
	Eastern equine encephalitis virus	High	NC	NC	NC	*C. lectularius*, (collected in pultry)	NC	[73]
	Kaeng Khoi virus	NS	1970 - 1971	Naturally	Gut	*Cimex insuetus*, *Stricticimex parvus*	Lopburi Province (Thailand)	[89]

NC: Not confirmed; NP: Not performed. [a]: Pathogenicity categorized in High (risk of infectious diseases), Middle (few reports), and NS (no significance); [b]: Experimentally, studies with experimental colonies of Cimicids. Naturally, reports of infectivity in wild Cimicids; [c]: Part of the body where the microorganisms were found in the Cimicid.

C. adjunctus: *Cimex adjunctus; Oeciacus vicarius*: *O. vicarius*

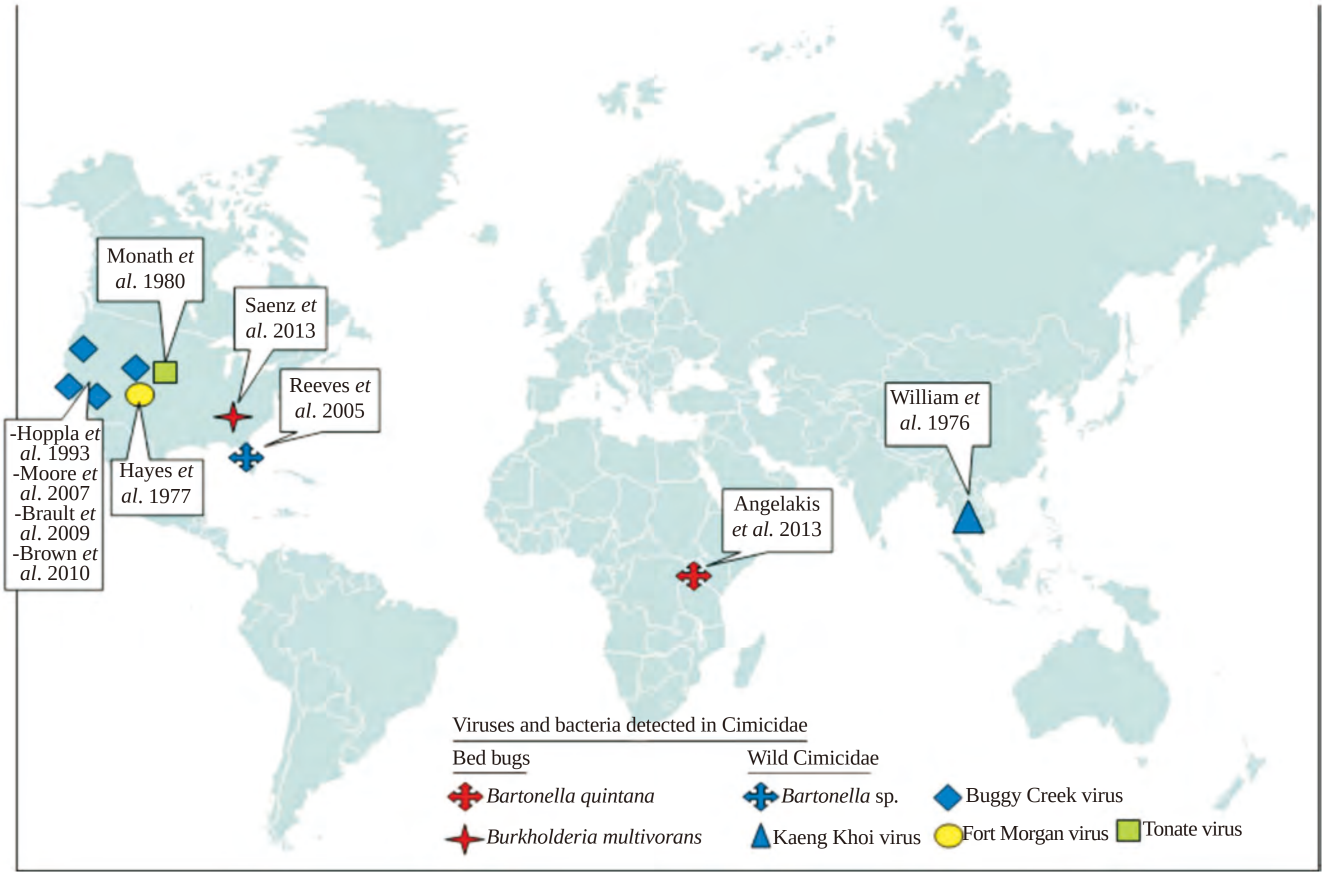

Figure 5. Distribution of reported transmissible pathogens found in Cimicidae.

persisted in the gut for no more than one day[92].

According to the microbial surveys summarized in the Table 2, we highlight the fact that there are no reports of isolations of microbes on the proboscis of *Cimex*. In most of the studies referenced, researchers were capable to isolate microorganisms from gut, salivary glands, integument or surface, feces, male or female reproductive organs, and others from whole body homogenate.

Moreover, almost all infectious agents studied experimentally on *Cimex*, were only transmissible under certain laboratory conditions and are only persistent within the intestinal cavity and without a reproductive cycle. Therefore there is not a big chance of infectivity, as also revealed with molecular techniques. However, some cimicids are able to transmit infectious agents mechanically through the bite wound in a wild manner. Many of the studies on this topic have used the species *O. vicarius* because it is the only one considered as a wild temporal vector of arboviruses[73]. Birds are reservoir of other arboviruses (*e.g.* West Nile virus) but a recent study has shown that Cimicidae are not implicated in its transmission[93].

T. cruzi has been the pathogen most studied experimentally on *C. lectularius* due to the health implications as the etiologic agent of Chagas' disease in tropical countries of the Americas. Historically, Hemiptera has been a well-described arthropod order recognized for being vector of multiple infectious diseases. *Triatoma* and *Cimex*, are two genus that share similar qualities, and regarding the ability to transmit *T. cruzi*, this similarity is in discussion yet. Recently, Salazar and colleagues made an experimental study concluded that quatitative bedbug defecation measures of *T. cruzi* were similar to those of important triatominae vectors, and even the authors showed efficient and bidirectional transmission of *T. cruzi*[65].

Among the most recent and important transmissible pathogens are *S. epidermidis*, *Staphylococcus arlettae*, *K. kristinae* and other antibiotic-resistant microorganisms[76]. In a recent letter to the editor published by Lowe & Romney, researchers collected five bedbugs from an infested, impoverished community in Vancouver, Canada, three of which were infected with methicillin-resistant *Staphylococcus aureus* and two with vancomycin-resistant *Enterococcus faecium*. The authors raised the hypothesis of pathogen transmission due to the feeding off infected blood and further concluded that infestations are a low-income housing problematic[94]. Nevertheless, the transmission of antibiotic-resistant pathogens has been strongly refuted[95].

On the other hand, there are other microbial agents that have acquired symbiotic relation with bedbugs[90]. Among them the genus *Wolbachia* has a high prevalence in Cimicidae. It is known that most endosymbiotic bacteria are transmitted between generations through transovarial mechanisms to facilitate blood digestion[1,74]. According to recent studies, actions against bedbugs' microbiota, such as the use of antibiotics, may improve the methods to control proliferation.

6.3. Economic impact and control

Different economic sectors have been affected by the innumerable local infestations. Among the most affected ones are the hotel and private housing investment industries. They are affected by the pest control expenses and the social reputation damages. Currently pest control methods are based on pyrethroids, or carbamates, insect hormone analogs, and organophosphates in some countries as malathion[96]. However, some Cimicidae species have not just acquired resistance to widely known organochlorine DDT, but to other insect groups[97,98].

The bedbug control needs a serious organization and collaboration between owner, tenant, pest controller and public health service. There are several steps in the control of bedbugs infestation. The first one is to be sure that the causative insects are bedbugs. After this, it is important to estimate the infestation level (approximate number of bedbugs and infested furniture and rooms), the narrowness of the environment: obstruction of the rooms (furniture, books, clothes, and others) and its size: isolated house, social habitat or hotel. In the last case, it is necessary to investigate the apartment, or hotel bedroom, in contact at the same floor and the floor above and below. The use of specially trained dogs is very effective for this detection step. Next step is a mechanical fight with vacuum, steamer, washing sheets and clothes at a temperature of 60 °C and to freeze all possibly infested objects and clothes which cannot be heat washed, at -20 °C for 72 h[99]. When the place is clean and obstructions removed, a chemical fight is useful when the infestation is important. Two treatments separated by seven days are necessary, because the eggs are resistant to insecticides. The current use of two or three different classes of insecticides is recommended because several bedbug populations are now resistant. Pyrethroids are widely used in place though there is significant resistance to this insecticide and that is even considered an important causative agent of toxic acute illnesses[70]. For a best efficacy, the remnant biocide chlorfenapyr belonging to pyrroles can be added. Other classes of insecticides used are carbamates, neonicotinoids and organophosphorus in some countries. Given the rapid evolution of insecticide resistance, it is likely that many different types or mixtures (*e.g.* pyrethroids plus neonicotoids) of insecticides are being used. Among Southeast Asian countries, there is also an organophosphorus formulation containing fenitrothion that has been registered against bedbugs in Malaysia.

When treatments are finished, it is necessary to assess the efficacy. The simple method is to monitor new bites on people; after about one month without bite, we can consider that the treatment is a success. Help of training dogs is used now in many countries and may be a quicker solution for evaluation.

7. Discussion

The greater number of infestations recorded in the world resurgence map of *Cimex* (Figure 2), has been a result of many factors, but the first implicated is the international tourism and travels which certainly increased in the mid-1990s with internet development, a facilitating tool of access to best price and choice of airline companies. Secondly, there is the poverty (treatments are expensive), the lack of adequate knowledge of the best control practices and the high population density. In north countries, DDT was used after World War II and forbidden in 1972[97]. Now people often use specific traps for pests, to kill just one species (cockroach, ants, and others), for instance pheromones-base traps. This was in favor of bedbugs increase and it in one of the explanation for their resurgence. In Africa and South Asia, infestation exists but seems to be less serious, may be due to the WHO Global Malaria Control Program based on spraying insecticide in houses of many villages and the donation of impregnated bed net for sleeping under cover of mosquitoes. These methods are efficient on bedbugs too but induce resistance to insecticide.

In this review, we want to denote the low impact of *Cimex* on public health in Latin American countries over the past decade. There were very few reports in South America about the resurgence of *Cimex*, and the controlled status of *Cimex* could even be postulated to be due to the fast interventions and techniques of the people in the region. Particularly, in Colombia there are very unusual ways to avoid the propagation of *Cimex*, where people have been using heat through fire with fuel, oil or other hydrocarbons. In addition, there is a program of vector control against kissing bugs (Triatominae), vectors of *T. cruzi* (etiologic agent of Chagas disease): between 1991 and 2004, all the countries of South and Central America joined together in the Southern Cone Initiative for elimination of domestic triatomines in villages, using pesticides (pyrethrinoids)[100]. This kind of fight could be efficient on bedbugs and might have contributed to eradication or control of bedbugs too.

Bedbugs are even a defining factor in some industries and their presence can haunt a person's subconscious for a long time. Moreover there are a lot of unresolved issues regarding their role in the transmission of infectious diseases, which leads to the question addressed in this review.

Wild Cimicidae (*O. vicarius*, *C. adjunctus*, *Stricticimex parvus*, *Cimex insuetus*) have been able to transmit arboviruses to birds, bats, humans for the last two decades[73]. In Missouri, (the USA), *C. adjunctus* was found associated with *Ornithodoros kelleyi* (bat ticks, Argasidae) in houses previously infested by bats[101]. Bat bugs and bird bugs can also enter homes when the resting places are located under the roof for example[18].

These examples suggest the high potential as vectors of certain bedbugs species, despite that *Cimex* species are not associated to the transmission of infectious diseases yet. The world of arboviruses is currently undergoing modifications (Dengue, Chikungunya, Zika, and others) and some of the ones are relatives to Cimicidae arboviruses[73].

Some bedbugs live in human houses and similar environments and the wide eclecticism of animal hosts (mammals, birds, bats) in *C. lectularius* and *C. hemipterus* (1) may conduct them to share blood meal on a wild or domestic animal with a wild species of Cimicidae or an arthropod vector.

The epidemiological relevance of Cimicidae in public health constitutes an important concern because over time these bedbugs have achieved an alarming infestation rate with an enormous sanitary impact. The quality of life of specific world population has been the most affected by this emerging global plague (Table 1). There are documented cases of insecticide resistance, sanitary emergencies and reports of emerging outbreaks. There is also a search of alternatives to eradicate and control bedbugs proliferation via mechanisms similar to the conventional and chemical ones, such as change of furniture and clothing. Additionally, periodic studies about the possible transmission of pathogenic microorganisms from wild Cimicidae to humans are suggested. The current situation, with its upward trend and challenges begs for a more careful study of these insects and the innumerable situations they might bring.

The role of bedbugs as vectors could be possible when an epidemic disease occurs, such as trench fever in Rwanda caused by *B. quintana* transmitted by body lice. In this case and, as explained by Blow *et al*., bedbugs could be mechanical vectors with possible contamination by crushing or human contact with their feces. When engorged, bedbugs are fragile and slightly sclerotized, above all in the stages one to three (Figure 4). So in this case, transmission mode could be equal than body lice. Angelakis *et al*.[43] detected DNA of *B. quintana* in *C. hemipterus* body. Future research must check whether *B. quintana* is alive in gut and/or feces. If the results are positive in case of epidemic disease with possible co-infestation by body lice/bedbugs, bedbugs could act as secondary vectors. Interestingly, *Cimex* can bite different people in a same room and reach another room easier and quicker than lice.

Bartonella spp. are commonly found in bats[102], and is not surprising because there is an old association of *Bartonella* and bedbugs with bats. These associations have always existed in wild species of Cimicidae as *C. adjunctus*[78], and *Bartonella* spp. in bats. Besides, Goddard *et al*'s experiments, consisting in *C. lectularius* inoculated with *R. parkeri*, should be continued with a larger number of bedbugs and other Rickettsia species before concluding a possible association[71].

In summary, we consider there is not enough evidence to establish a definite role of bedbugs as vectors for the moment but future research with bacteria, such as *Bartonella* spp., could give to bedbugs a similar vector status as body lice, and for the case of *T. cruzi* is not discarded similar status as triatomines.

Conflict of interest statement

We declare that we have no conflict of interest.

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