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Trends in Human Fecal Carriage of Extended-Spectrum β-Lactamases in the Community: Toward the Globalization of CTX-M

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SUMMARY

In the last 10 years, extended-spectrum β-lactamase-producing enterobacteria (ESBL-E) have become one of the main challenges for antibiotic treatment of enterobacterial infections, largely because of the current CTX-M enzyme pandemic. However, most studies have focused on hospitalized patients, though today it appears that the community is strongly affected as well. We therefore decided to devote our investigation to trends in ESBL-E fecal carriage rates and comprehensively reviewed data from studies conducted on healthy populations in various parts of the world. We show that (i) community ESBL-E fecal carriage, which was unknown before the turn of the millennium, has since increased significantly everywhere, with developing countries being the most affected; (ii) intercontinental travel may have emphasized and globalized the issue; and (iii) CTX-M enzymes, especially CTX-M-15, are the dominant type of ESBL. Altogether, these results suggest that CTX-M carriage is evolving toward a global pandemic but is still insufficiently described. Only a better knowledge of its dynamics and biology will lead to further development of appropriate control measures.

INTRODUCTION

The first strains of extended-spectrum beta-lactamase-producing enterobacteria (ESBL-E) were reported at the beginning of the 1980s (1), shortly after the release of broad-spectrum cephalosporins for clinical use (2). In the 1980s and -90s, ESBL were produced mostly by *Klebsiella* spp. and *Enterobacter* spp. and were encoded by genes derived through mutations of the ubiquitous plasmid-borne bla_{TEM} and bla_{SHV} wild-type penicillinase genes (3, 4). These early ESBL-E were observed almost exclusively in hospitals, first in Europe and subsequently in other parts of the world (5), especially in intensive care units (ICU), where they sometimes generated large-scale outbreaks (6).

Twenty years later, in the late 1990s, soon after the patents of extended-spectrum cephalosporins fell into the public domain and generics were flourishing, community-acquired infections due to ESBL-E emerged, mainly as urinary tract infections (UTI) (7). Among the very wide variety of enzymes exhibiting ESBL activity (8), class A beta-lactamases have had particular epidemiological success. These enzymes hydrolyze penicillins, oxyiminocephalosporins, and aztreonam to various degrees, but they spare carbapenems and cephamycins. The emergence of community-acquired ESBL-E infections was associated with two major epidemiological changes. First, unlike ESBL-E previously isolated in hospitals, the strains responsible for community-acquired infections were mostly strains of *Escherichia coli*, a species which is both a normal intestinal commensal in humans and a major pathogen (9). Second, they produced CTX-M enzymes, a group of ESBL that are highly divergent from TEM- and SHV-derived mutants, initially named because of their particular affinity for cefotaxime (10). bla_{CTX-M} genes, most probably mobilized from the chromosomes of environmental bacteria belonging to various species of

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the *Kluyvera* genus (11), have repeatedly moved to plasmids well adapted to *E. coli* (12). Currently, 136 CTX-M alleles have been identified. They are divided into 5 groups according to their different progenitor species. This can be compared to the greater diversity associated with the 208 and 173 mutants of TEM and SHV, respectively (http://www.lahey.org/Studies/; accessed 12 April 2013). Strikingly, CTX-M enzymes have rapidly supplanted TEM- and SHV-derived ESBL, even in hospitals (13), although what has endowed them with such an obvious epidemiological advantage is not yet understood. What is also worrisome is that ESBL-E often show multiple coresistance (13), complicating first-line treatment of many frequent community infections, such as UTI (14). For severe ESBL-E infections, carbapenems have become the drugs of choice (15), which is cumbersome because these antibiotics are for parenteral use only and thus are difficult to administer and often unavailable in low-resource countries, where the incidence of ESBL-E infections is particularly high (16).

The digestive tract is the main reservoir from which enterobacteria originate, whatever the type (community or hospital acquired) of infection (17, 18). It is also a melting pot where exchanges of resistance genes occur and antibiotic treatments select for the overgrowth of resistant bacteria (19). Fecal carriage of ESBL-E in the community was first reported in Spain and Poland, in 2001 and 2002, respectively (20, 21). Many other reports describing wide differences in carriage rates have since been published, suggesting dissimilarities in the levels and dynamics of ESBL-E epidemiology between geographic areas. However, as far as we know, the literature on ESBL-E community carriage rates has never been reviewed comprehensively, making it difficult to compose a global picture.

In this work, studies published in the English and French literature were grouped together according to World Health Organization (WHO) geographical areas (http://www.who.int/healthinfo/global_burden_disease/definition_regions/en/index.html; accessed 18 December 2012), and temporal trends were analyzed according to the year of sampling.

GLOBAL DISSEMINATION AND DISTRIBUTION

In all areas, the reported rates of ESBL-E community carriage were almost always under 10% before 2008 but often higher afterwards (Fig. 1). In 2008, the carriage rate skyrocketed to over 60% for the first time, in Thailand (22).

Although increasing over time everywhere, carriage of ESBL-E did not evolve with the same dynamics (Fig. 1). Large intra- and interregional variations have been observed. Reports from the Western Pacific, Eastern Mediterranean, and Southeast Asia regions showed the highest carriage rates and the most striking recent ascending trends. In contrast, rates reported in Europe never exceeded 10%, with the exception of a recent report of 11.6% observed in 2011 among patients upon admission to a geriatric unit in Belgium (23).

Because the countries where these data were obtained have populations that differ considerably, the data do not adequately reflect the magnitude of the problem, i.e., the number of carriers worldwide. Figure 2 shows the number of ESBL-E carriers estimated for 2010, according to the data analyzed in this review and the WHO 2010 population census (http://www.who.int/research; accessed 18 December 2012). Strikingly, over 1.1 billion ESBL-E carriers appear to be present in the community populations of Southeast Asia. The Western Pacific and Eastern Mediterranean regions rank second and third, with 280 and 180 million carriers, respectively, ahead of Africa, where 110 million carriers are estimated to be present. America and Europe appear to be far behind, with 48 and 35 million carriers, respectively (Fig. 2). This ranking suggests that poor access to drinking water, poverty, and a high population density are extremely efficient driving forces for ESBL-E dissemination, as is the case for any fecally-orally transmitted diseases. Indeed, the role of water pollution as a major reservoir for ESBL-E dissemination has been well documented. This has been the case not only for wastewater in China (24), the Czech Republic (25), Austria (26), India (27), Brazil (28), and Congo (29) but also for many rivers or aquatic ecosystems. ESBL-E have indeed been isolated from well water in Nicaragua (30) and from diverse other aquatic environments in Switzerland (31), the United Kingdom (32), China (33), South Korea (34), Portugal (35), and Tunisia (36). Even seawater from beaches in Algeria (37) and water from the Antarctic have been found to be positive for ESBL-E (38), suggesting that the current reservoir of these bacteria is in reality massive (Fig. 3). Human activities such as those associated with farming and food chain production may be at the root of ESBL-E dissemination, as recently reviewed (39) (Fig. 3). Surprisingly, the rates of colonization in Switzerland in 2012 were as high as 15% in pigs and 63% in chickens (40), despite the rather strict antibiotic policy in that country (41). *E. coli* was the predominant colonizing species, and CTX-M enzymes were the most frequent ESBL. The spread of ESBL strains from

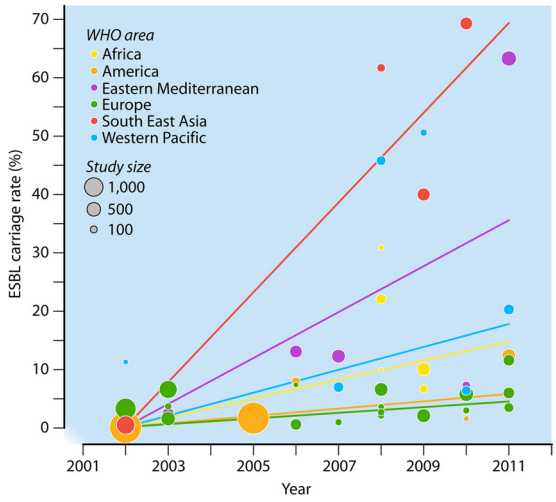

FIG 1 ESBL carriage rates in the community, according to their geographical and temporal distribution. Each bubble area is proportional to the size of the corresponding study. The lines represent the evolution of ESBL-E carriage rates over time for each geographical area, as established by a weighted linear regression model using the values reported in the literature from 2002 to 2011. Over this period, ESBL-E carriage increased significantly in all regions, with differences within regions. In Europe, the ESBL-E carriage rate increased significantly by 0.5% per year from 2002 to 2011 (95% confidence interval [95% CI] = 0.04% to 0.90%; $P = 0.03$). Compared to the rise in Europe, the progression rate was not different in Africa (difference in annual progression compared to that in Europe, +1.1% [95% CI = −0.4% to 2.7%]; $P = 0.1$) or America (+0.1% [95% CI = −0.6% to 0.9%]; $P = 0.7$) but was significantly higher in Southeast Asia (+7.2% [95% CI = 5.1% to 9.2%]; $P < 10^{-7}$), the Eastern Mediterranean region (+3.5% [95% CI = 2.0% to 4.9%]; $P < 10^{-4}$), and the Western Pacific region (+1.5% [95% CI = 0.04% to 2.90%]; $P = 0.04$). The differences in rate increases between Southeast Asia, the Eastern Mediterranean region, and the Western Pacific region were all significant.

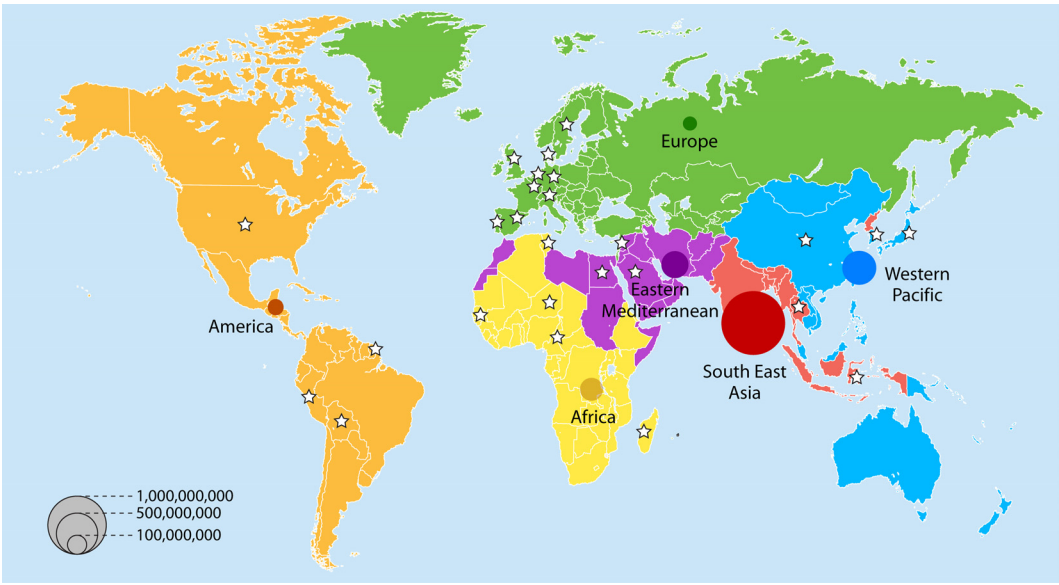

FIG 2 Number of ESBL carriers in the community in 2010, according to WHO region grouping. The 6 WHO regions are represented by different colors. WHO estimates of the population of each geographic area in 2010 (http://www.who.int/research; accessed 18 December 2012) were used to compute the number of ESBL-E carriers. ESBL carrier rates were established using the model presented in Fig. 1 for the year 2010. Stars represent countries with available data for modeling. Each bubble area is proportional to the estimated number of ESBL carriers in that region.

animals to humans via the food industry is now strongly suggested by genetic comparisons of strains from both settings (42, 43). Finally, pets are also involved, as suggested by reports from Portugal on healthy animal carriers (44) and by reports on infected animals in the United States (45), China (46), and Switzerland (47). Transmission from pets to humans is suggested when the genetic backgrounds of the strains and CTX-M alleles are compared (48, 49), but a human-to-pet route of transmission has also been proposed (50) (Fig. 3). In addition, the dissemination of some strains may be restricted to pets, as suggested by a recent study describing specific *Klebsiella pneumoniae* clones with their own genetic ESBL plasmids that have been isolated exclusively from companion animals (51).

REGIONAL SPECIFICITIES

Europe

As mentioned previously, Europe is the area where community ESBL-E were first described, in 2001, in outpatients in Spain (21) and a cohort of healthy children in Poland (20). Fine characterization of ESBL types was not performed, but an association with *E. coli* was underlined in the Spanish study, which contrasted with the predominance of ESBL-producing *K. pneumoniae* strains in hospitals at that time. In the Polish study, MICs of cefotaxime for the strains were higher than those of ceftazidime, suggesting that the isolates were actually of the CTX-M type (52). Clearly, these features forecasted those that were going to be described later. Spanish teams were also the first to report the gradual rise in carriage rates in the community (53, 54) and to point out the role of the community as a reservoir possibly maintained by transfer from contaminated food (55, 56). In 2008, they reported the first evidence of dissemination of carriage between household members (57) and showed that contact with patients with ESBL-E UTI was a risk factor for carriage (58). Elsewhere in Europe, carriage rates were lower than those in Spain and remained below 5% (59–64). However, this may be changing, as suggested by recent studies performed in Switzerland and France (65, 66). Aging populations may also be at particular risk (23, 67). Differences in carriage rates have been reported between residents of the United Kingdom belonging to various ethnic groups (68), which might reflect differences in contacts with subjects from countries of high prevalence. The predominant allele appears to be CTX-M-15, as documented in France (67, 69), the United Kingdom (63), and Switzerland (65). However, the Spanish epidemiology seems to have specific characteristics, with a predominance of CTX-M-9 and CTX-M-14 alleles (Table 1). This could be linked to different migration trends.

Eastern Mediterranean

The first data from the Eastern Mediterranean region were published in 2005. They reported an ESBL carriage rate of 2.4% in young healthy students (70), pointing out the community nature of the pandemic early. Since then, carriage rates have ranged from 7.3% in Tunisia in 2010 (71) to 63.3% in Egypt in 2011 (72), reflecting the sharp increase and wide variations in carriage rates in this area. The very scarce CTX-M enzymes identified were of alleles 1 and 15 (Table 1).

Africa

Community carriage in Africa has been studied very poorly. Reported rates appear to be quite high, from 10.0% in Senegal (73) to 30.9% in Niger (74). Poor populations were found to be particularly affected in Madagascar in 2009 (75). Both there (76) and in Niger (74), it was shown that children were often carrying ESBL-E upon admission to hospital. Moreover, antibiotic use and hygiene failures in hospitals further dramatically increased transmission and dissemination among patients. In cases where they were identified, CTX-M enzymes were practically exclusively of allele 15 (Table 1).

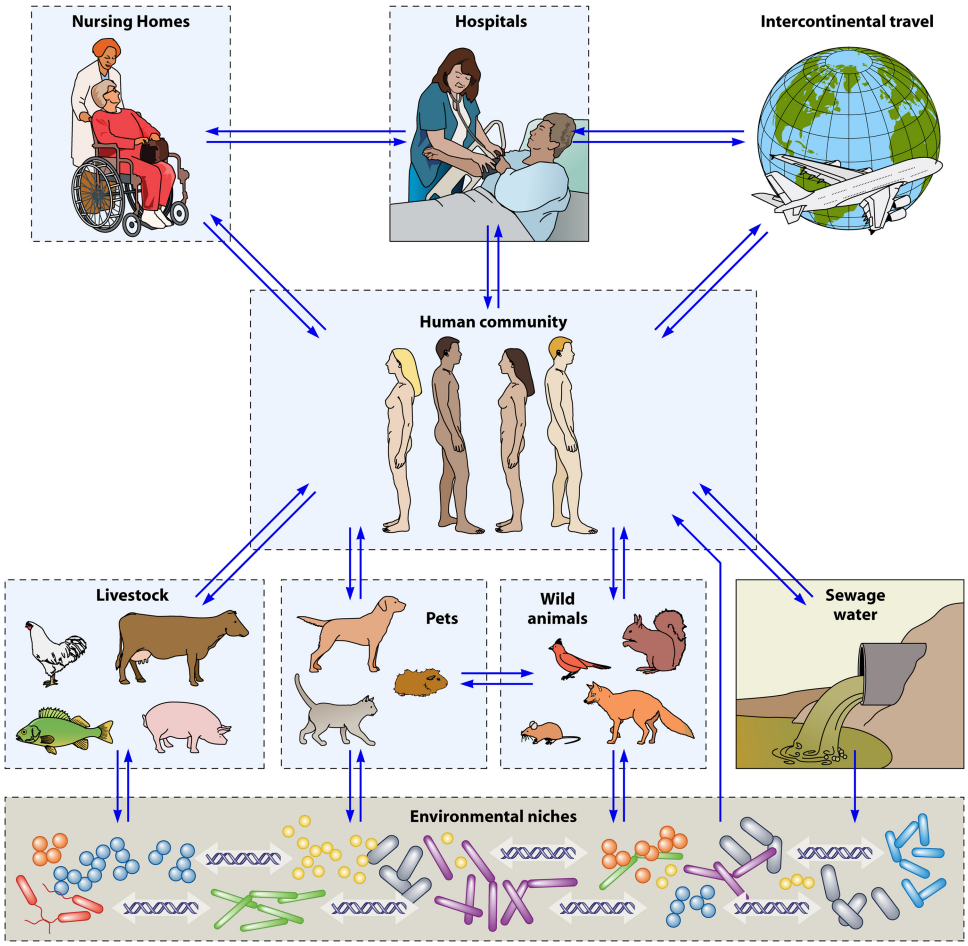

FIG 3 Representation of the main digestive or environmental reservoirs of ESBL-E to which the worldwide human community belongs and is also exposed. Each independent reservoir is included in a dashed black outline, inside which cross-transmission may occur. Arrows show the flux of ESBL-E from one reservoir to another. Environmental niches comprise mainly water, soils, and plants, where genetic material exchanges between bacteria of digestive and/or environmental origin occur.

Southeast Asia

The first report from Southeast Asia—from Java in 2001 to 2002— detected no community carriage (77). However, this study had technical limitations. Only predominant fecal enterobacteria were studied, and the subjects included were from a single area. Since then, data from rural Thailand have indicated very high rates, reaching 69.3% in 2010 (78). Interestingly, in another study from Thailand, there were significant variations in carriage rates between subjects from three separate provinces. These differences seemed to be linked to variations in overall antibiotic use between these populations but not to individual risk factors (79). The great majority of CTX-M alleles identified in Thailand belonged to group 9. However, data from Indonesia reported the presence of alleles 14 and 15 as early as 2001 to 2002 (Table 1). Data from other countries in the region, including India, are lacking.

Western Pacific

The number of studies available from the Western Pacific region is strikingly low considering the diversity and size of the populations living in this region. Wide differences are reported in two studies available from China, ranging from 7% in Shenyang in 2007 to 50% in Fujian in 2009 (80, 81). This underscores the magnitude of the variations that can be observed between areas and populations in such a vast country. Available data clearly indicate the predominance of the CTX-M-14 allele. Interestingly, CTX-M-15 ranks second in two recent studies from China, from 2007 and 2009, suggesting that this allele has now emerged there (Table 1).

The Americas

Carriage rates have been assessed repeatedly in poor children in urban areas in Latin America, which is of great interest. The carriage rate was as low as 0.1% in 2002 but jumped to 1.7% in 2005 and reached 12.4% in 2011 (82–84). Just as in the Thai study described above (79), no individual risk factor (including antibiotic intake) was associated with carriage (84). In contrast, this seemed to correlate with the overall exposure of the population to antibiotics, as observed in a remote community of Amerindians from French Guiana (85). Although the CTX-M-2 allele was predominant in early studies from South America, longitudinal data from Peru and Bolivia tend to demonstrate that CTX-M-15 is also emerging there, as in other regions (Table 1). Data from North America are virtually nonexistent, and to our knowledge, only the 24 U.S. cases explored in a study of travelers (86) could be considered community related, suggesting a 1.6% carriage rate (Table 1).

TABLE 1 Main results of the studies included in this work

WHO area[a]	Yr of study[b]	Country	No. of individuals included	ESBL carriage rate (% [no. of ESBL carriers])[c]	% of carriers with CTX-M-type ESBL (no. of positive results/ total no. of carriers)[d]	Species identified (no. with species/ total no. of carriers)[d,e,f]	CTX-M allele(s) identified (no. of isolates with allele/total no. of carriers)[d,g]	Clonality rate (%) (detection method)[d,h]	ST identified[d]	Independent risk factor(s) identified (by multivariate model)[d]	Subjects[e]	Reference
Europe	1999	France	517	0 (0)	NA	NA	NA	NA	NP	NP	Army recruits	61
	2001–2002	Spain	1,321	3.3 (44)	75 (33/44)	**Ecol** (42/44), Pmir, Eclo	**9** (18/33), 14, 15, 29, 1, 3, 34	NP	NP	NP	Emergency patients	56
	2003	UK	565	1.6 (9)	100 (9/9)	**Ecol** (8/9), Salm spp.	**15** (4/9), 14, 9	None (RAPD)	NP	NP	General practice patients	63
	2003	Spain	108	3.7 (4)	50 (2/4)	**Ecol**	14, 2-like	None (PFGE)	NP	NP	Healthy individuals	54
	2003	Spain	948	6.6 (63)	NP	**Ecol** (73/75), Kp, Ckos	NP	NP	NP	NP	Emergency patients	55
	2005–2006	Spain	54	7.4 (4)	50.0 (2/4)	**Ecol**	**14**	None (rep, PFGE)	NP	NP	Healthy individuals (controls of a case-control study)	57
	2006	France	332	0.6 (2)	0 (0/2)	NA	NA	NA	NA	NA	Healthy individuals	62
	2007	Spain	105	6.7 (7)	85.7 (6/7)	**Ecol**	**1** (2/6), 14a, 14b, 8, 32	NP	NP	NP	Healthy individuals, only Ecol studied	145
	2007–2008	Portugal	112	2.7 (3)	33.3 (1/3)	**Ecol**	**1**	NP	NP	NP	Healthy children, only Ecol studied	59
	2008	Denmark	84	3.6 (3)	100 (3/3)	**Ecol**	**14a**	2/3 in 1 clone (ST1631) (MLST, PFGE)	1631, 641	None identified	Army recruits	60
	2008	Sweden	96	2.1 (2)	93.8 (15/16)	**Ecol**	**1** (11/15), 9	None (rep, serotyping)	NP	None identified	Healthy individuals	64
	2010	Sweden	100	3.0 (3)		**Ecol**						
	2008	France	500	6.6 (33)	78.8 (26/33)	**Ecol** (21/26), Kp, Eclo	**15** (11/26), 1, 14, 65, 27	3/28 in 1 clone (rep)	NP	Previous carriage, antibiotic use during the last 3 months	Patients with first admission to hospital	67
	2009	France	517	2.1 (11)	90.1 (10/11)	**Ecol** (9/10), Kp	**15** (3/10), **61** (3/10), 2, 27, 14	None (PFGE)	NP	NP	Army recruits	61
	2010	Switzerland	586	5.8 (34)	97.1 (33/34)	**Ecol**	**15** (14/33), 1, 14, 2	3*2 and 1*3 clones (serotyping)	NP	NP	Healthy individuals	65
	2010–2011	Belgium	337	11.6 (39)	71.8 (28/39)	**Ecol** (39/45), Kp, Ent spp., Cit spp.	Group 1 predominant	NP	NP	Multiple contacts with hospital over 1 year (long term)	Geriatric unit admission	23
	2011	Germany	231	3.5 (8)	NP	**Ecol**	NP	NP	NP	Travel to Greece and Africa during the past 12 months, domestic animals	Participants in a symposium	146
	2011	France	345	6 (21)	86 (18/21)	**Ecol**	**15** (7/18), **1** (7/18), 14, 2	4/18 in 2 clones (361 and 131) (MLST, PFGE)	156, 10, 167, 744, 34, 210, 216, 1125, 155, 95, 131, 141, 69, 120, 5211, 2439	None	Healthy individuals	69

Eastern Mediterranean	2003	Lebanon	382	2.4 (9)	100 (9/9)	**Ecol**	**15**	None (MLST)	NP	NP	Healthy students	70
	2006	Saudi Arabia	426	13.1 (56)	NP	**Ecol** (52/56), Kp	NP	NP	NP	NP	Healthy students, only Ecol and Kp were selected	147
	2006–2007	Saudi Arabia	505	12.3 (62)	NP	**Ecol** (?), Kp	NP	NP	NP	NP	Healthy individuals	148
	2009–2010	Tunisia	150	7.3 (11)	91.0 (10/11)	**Ecol**	**1**	3/10 in 1 clone (ST58) (PFGE, MLST)	165, 57, 155, 58, 10, 48, 398, 219	NP	Healthy individuals	71
	2010–2011	Egypt	632	63.3 (400)	NP	**Ecol** (285/400), Kp, Ko, Ent spp.	NP	NP	NP	NP	Healthy individuals	72
Africa	2007–2008	Niger	55	30.9 (17)	90.9 (20/22)	**Ecol** (13/20), Kp, Eclo, Easb	**15**	3/17 in 1 Ecol clone (ST361) (rep, PFGE, MLST)	361, 354, 5, 131, 10, 101, 68, 448, 196, 617, 410	NP	Pediatric admission	74
	2008*	Senegal	20	10.0 (2)	100 (2/2)	**Ecol**	**15**	100 (2/2) (rep)	NP	NP	Healthy children	73
	2008	Madagascar	244	22.1 (54)	NP	**Ecol** (24/54), **Kp** (24/54), Eclo, other EB	NP	NP	NP	Hospitalization during the last 30 days	Pediatric admissions	76
	2009	Madagascar	484	10.1 (49)	94.2 (49/52)	**Ecol** (31/49), Kp, Eclo, Cf, Klu, Pan	**15** (46/49), 3, 1	8/53 in 3 Ecol clones (rep, ERIC)	NP	Unemployment	Healthy individuals	75
	2009	Cameroon	150	6.7 (10)	100 (10/10)	**Ecol** (9/10), Kp	**15**	NP	NP	None	Healthy students	149
Southeast Asia	2001–2002	Indonesia	1,998	0 (0/1,998)	NA	NA	NA	NA	NP	NP	Healthy individuals, only the dominant flora was studied	77
	2008	Thailand	160	61.7 (87)	94.3 (82/87)	**Ecol** (73/82), Cit spp., Kp, Ent spp., Salm spp., other EB	**Group 9** (71/82), group 1	NP	NP	NP	Healthy individuals	22
	2009	Thailand	445	40 (177)	92.7 (164/177)	**Ecol** (149/164), Cit spp., other	**Group 9** (127/164), group 1, group 8	NP	NP	Antibiotic exposure (?)	Healthy individuals	79
	2010	Thailand	417	69.3 (289)	94.8 (274/289)	**Ecol** (234/274), Kp, Cit spp., Ent spp.	**Group 9** (166/274), group 1, group 8	NP	NP	Formal education, hospitalization over past year, antibiotic use during last 3 months	Healthy individuals	78
Western Pacific region	2002	China	53	11.3 (6)	100 (6/6)	**Kp** (4/6), Ecol	**24** (2/6), **38** (2/6), 9, 14	4/6 in 2 clones (PFGE)	NP	NP	Healthy students	150
	2007*	China	270	7.0 (19)	100 (19/19)	**Ecol**	**14** (11/19), 22, 79, 24	None (PFGE)	NP	Antibiotic use in past <3 months	Elderly people	81
	2007–2008	China	225	45.8 (103)	95.4 (104/109)	**Ecol** (88/109), Kp	**14** (65/104), 15, 3, 24, 27, 55, 57	15/109 in 6 clones (PFGE)	NP	Amount of living space per person	Pediatric admissions and household contacts	98
	2009	China	109	50.6 (55)	100 (55/55)	**Ecol**	**14** (39/55), 15, 55, 79, 3, 24, 27	None (PFGE)	NP	NP	Healthy individuals	80
	2009–2010	Japan	218	6.4 (14)	92.9 (13/14)	**Ecol** (11/13), Kp	**14** (5/13), 2, 8, 3, 15	NP	NP	None	Healthy individuals	151
	2011	Korea	290	20.3 (59)	NP	**Ecol** (57/59), Kp	NP	NP	NP	NP	Healthy individuals	152

(Continued on following page)

TABLE 1 (Continued)

WHO area[a]	Yr of study[b]	Country	No. of individuals included	ESBL carriage rate (% [no. of ESBL carriers])[c]	% of carriers with CTX-M-type ESBL (no. of positive results/ total no. of carriers)[d]	Species identified (no. with species/ total no. of carriers)[d,e,f]	CTX-M allele(s) identified (no. of isolates with allele/total no. of carriers)[d,g]	Clonality rate (%) (detection method)[d,h]	ST identified[d]	Independent risk factor(s) identified (by multivariate model)[d]	Subjects[e]	Reference
The Americas	2002	Bolivia and Peru	3,208	0.1 (4)	100 (4/4)	**Ecol**	**2** (3/4), 15	NP	NP	NP	Healthy children, only Ecol was selected	83
	2005	Bolivia and Peru	3,193	1.7 (50)	88.0 (44/50)	**Ecol**	**2** (16/44), 15, 14, 24, 56	19/44 in 6 clones (RAPD)	NP	NP	Healthy children, only Ecol was selected	153
	2006	French Guiana	163	8.0 (13)	86.0 (12/14)	**Ecol**	**2** (11/15), 8	9/14 in 2 clones (rep)	NP	Overall antibiotic pressure (?)	Healthy individuals	85
	2011	Bolivia and Peru	482	12.4 (60)	96.7 (58/60)	**Ecol**	**15** (23/58), 65, 8, 14, 2, 3	25/58 in 9 clones (RAPD)	NP	Antibiotic use	Healthy children, only Ecol was selected	84
Travelers	2006–2008	UK	1,031	17.7# (182)	100 (182/182)	**Ecol**	**15** (174/182), group 9, group 2	1 clone of 21 ST131 clones identified (MLST, PFGE)	Only ST131 strains were detected	NP	Travelers with diarrhea	89
	2007–2008	Sweden	101 (before)	1.0 (1)	100 (24/24)	**Ecol**	**15** (13/24), 14, 9, 27, 1	NP	NP	Visiting India, gastroenteritis	Travelers (before versus after travel)	91
			100 (after)	24.0# (24)								
	2008	Sweden	242	24.0# (58)	90 (52/58)	**Ecol**	**Group 1** (35/ 52), group 9	None (rep)	NP	Travel, excluding Europe (Egypt, Thailand, India, Middle East, Southeast Asia)	Travelers with diarrhea	90
	2009–2010	USA	60 (before)	1.6 (1)	NP	NP	NP	NP	NA	NP	Travelers (before versus after travel)	86
			28 (after)	25.0 (7)	71.4 (5/7)	**Ecol**	**14** (3/5), 15	None (MLST)	39, 8, 37, 399, 8, 437,83	NP		

[a] Studies were grouped together according to WHO geographical areas (http://www.who.int/healthinfo/global_burden_disease/definition_regions/en/index.html; accessed 18 December 2012).

[b] *, studies in which the year of sampling was not specified. In those cases, the year indicated is the year before the year of publication.

[c] #, the carriage rate value was not included in the statistical analysis.

[d] NA, not applicable; NP, not performed.

[e] Ecol, *Escherichia coli*; Salm, *Salmonella*; Pmir, *Proteus mirabilis*; Eclo, *Enterobacter cloacae*; Kp, *Klebsiella pneumoniae*; Ckos, *Citrobacter koseri*; Ent, *Enterobacter*; Cit, *Citrobacter*; Ko, *Klebsiella oxytoca*; EB, *Enterobacteriaceae*; Cf, *Citrobacter freundii*; Klu, *Kluyvera*; Pan, *Pantoea*; Easb, *Enterobacter asburiae*.

[f] The dominant enterobacterial species is shown in bold. The dominant species is either the dominant species among CTX-M strains (when such data are known) or the dominant species among ESBL strains.

[g] The dominant allele or allelic group is shown in bold.

[h] RAPD, random amplification of polymorphic DNA; PFGE, pulsed-field gel electrophoresis; rep, repetitive element palindromic PCR; MLST, multilocus sequence typing; ERIC, enterobacterial repetitive intragenic consensus PCR.

This rate seems to be corroborated by the rather low hospital rates of ESBL carriage observed in neighboring Canada (87).

Travelers

Carriage rates in Europe are lower overall than those in other parts of the world, and carriage of resistant bacteria has been associated in the past with international travel (88). The suspicion thus emerged that travel of subjects from countries with low ESBL-E carriage rates to places with high ESBL-E carriage rates might be a source of colonization. Indeed, ESBL-E carriage rates in European subjects with traveler's diarrhea, upon return from diverse overseas areas, were 24% and 18% in 2006 and 2008, respectively (89, 90). These rates increased significantly after travel to Egypt, India, Southeast Asia, Thailand, and the Middle East (90). A prospective study of healthy subjects confirmed the high acquisition rates associated with travel to India, Asia, and the Middle East (91). Finally, in a prospective case-control study performed in 2008, European travelers had a 23% ESBL-E carriage rate, which was significantly more than the 4% found in nontravelers. Upon return from India, Africa, or Asia, the ESBL-E carriage rate reached 46% (92).

The duration of carriage after travel seems to be relatively short, lasting only a few weeks (93). This contrasts with the mean carriage duration of 6.6 months in patients who were colonized during hospitalization (94). However, carriage can be far more prolonged in travelers with diarrhea or exposed to antibiotics while abroad (93, 95) and in native African children arriving in Europe after adoption (96).

DISSEMINATION ROUTES, STRAIN DIVERSITY, AND TRANSMISSION

As mentioned above, dissemination within households was first demonstrated in a Spanish study, where carriage rates were found to be significantly higher among relatives of patients with ESBL-producing *E. coli* UTI than in nonrelative controls (23.8% versus 7.4%; $P < 0.01$) and possibly higher in household relatives than in nonhousehold ones (27.4% versus 15.6%; $P = 0.1$) (57). However, molecular characterization of the isolates showed that although there was a particular strain with a given ESBL allele disseminated between subjects in nearly half of the families, strains producing the same ESBL allele but with different genetic backgrounds were also found. This suggested to the authors that diverse modes of transmission of resistance were involved, with a possible major role of plasmids, as earlier suspected in hospital settings (97). Similar results were reported in another study, again from Spain, in which up to 66% of the isolates from patients with community-acquired ESBL-producing *E. coli* infections were indistinguishable from those isolated from fecal samples from their household members. Again, this suggested that patients with community infections and members of their households were a reservoir for ESBL-producing strains (58). In China, the carriage rates were higher in families with at least one individual with a history of out-of-town residence and were inversely correlated with living space (98). Finally, transmission of ESBL-E within the family does not seem to be limited to *E. coli* but may also occur for other enterobacteria, such as *Salmonella* (96).

Studies describing the genetic relatedness of ESBL-E isolates are limited, and different methods, including repetitive element palindromic PCR (rep-PCR), random amplification of polymorphic DNA (RAPD), and pulsed-field gel electrophoresis (PFGE), were used. It is clear, however, that diverse ESBL-producing *E. coli* clones are present in the community. No widely distributed clone appears to have emerged, in contrast with what has been described for infectious strains, where a pandemic clone, ST131, was pinpointed (66). The ST131 clone was, however, also sometimes found in carriers from Madagascar, India, and Pakistan (75, 89), and also in France (69) and Niger (74). Altogether, the general picture seems to be that each carrier has his/her own strain that disseminates exclusively in its immediate surroundings. This is in sharp contrast to what was observed in the 1980s and -90s, when TEM and SHV types of ESBL were prevalent and frequently caused clonal outbreaks in hospitalized patients, in whom the forces underpinning the dynamics of dissemination are different (6).

ENZYMES

In cases where they were analyzed, CTX-M alleles generally accounted for more than 90% of the ESBL-producing strains from community individuals (Table 1). Although there were some early studies which suggested that there was some degree of CTX-M allele specificity between regions, a trend toward the dominance of the CTX-M-15 allele appeared afterwards, except in the Western Pacific region, where CTX-M-14 continues to be the predominant allele (Table 1). It may be that specific biological properties are associated with this allele that could explain its propensity to disseminate, but this still remains to be elucidated fully.

HOW TO DEAL WITH CARRIERS UPON ADMISSION TO HOSPITAL

Despite the global extent of the pandemic, there are currently no precise guidelines about how to screen for and deal with ESBL-E carriers in hospitals (99). This is partially due to the paucity of studies on the efficacy of ESBL-E screening to ascertain the spread of hospital-acquired infections in nonoutbreak situations. Although this may be changing rapidly (100), the current situation is that recommendations regarding this issue are not homogeneous, even within a single geographic area (101). In hospitals, clonal outbreaks of CTX-M-producing *E. coli* have been described (102, 103) but are not frequent (104). This may be because the mode of dissemination of the current CTX-M-type ESBL genes is due more often to plasmids than to strain transmission and may go unnoticed and therefore underestimated (74). Currently, the type of unit to which the patient is admitted, the presence of risk factors, and/or the risk of environmental contamination is taken into account to define the best screening strategies.

In many hospitals, screening for ESBL-E carriage is systematic for ICU patients, and carriers are often administered carbapenems as empirical therapy for hospital-acquired infections. Another reason for systematic screening of ICU patients is that the likelihood of outbreaks is higher there than in other wards because of the very large number of medical procedures performed which promote indirect transmission of strains between patients (105). Although it has clearly been demonstrated that recent hospitalization or transfer, comorbidities, previous antibiotic treatment, urinary catheterization, and age are independently associated with ESBL-E carriage, the absence of any of these items does not guarantee the absence of ESBL-E carriage (106). Finally, patients likely to disseminate high loads of ESBL-producing strains in the environment (because of wounds, diarrhea, or secretions) should always be screened (107).

Once identified, ESBL-E carriers in most cases are isolated in

single rooms, where contact precautions are recommended to prevent cross-transmission. However, this is applied unevenly (101), and its effectiveness is debated (108). Apart from when the clone is particularly virulent or the surrounding patients are at particular risk (109), cohorting does not appear to be applied anymore.

At this time, systematic screening for ESBL-E carriage upon admission to hospital is not recommended. Systematic screening is costly, and its effectiveness and that of associated policies of isolation have not been demonstrated (110). In addition, the spread of ESBL-producing strains seems to be species dependent. For example, *Klebsiella pneumoniae* tends to be cross-transmitted more frequently than *E. coli* (111). In the context of a likely future increase in ESBL-E carriage, it is a commonly accepted view that strict adherence to standard contact precautions (107) by all medical and nonmedical staff members will be the cornerstone of the control of ESBL dissemination in hospitals. However, the topic is the subject of intense debate (112) and research. Things might change when rapid carriage detection methods that can be used on a large scale become available.

HOW TO PREVENT AND REDUCE ESBL CARRIAGE IN COMMUNITY POPULATIONS

We badly lack adequate recommendations to prevent the emergence and spread of ESBL-E through fecal carriage in the community. Interventions could be targeted at several levels. First, one could try to reduce the circulation of resistant bacteria in the environment where they circulate. This would join with general efforts for better water sanitation, which is far beyond the scope of this review. It is notable that transmission of antimicrobial resistance is not currently listed in the *Water Quality and Health Strategy 2013–2020* report from WHO (113). However, it has been shown that urban wastewater treatment plants are hot spots for antibiotic-resistant bacteria and genes spread into the environment (114). Hospital effluents may be a vehicle for ESBL-E (115). Methods to reduce resistant bacterial loads in wastewater and the amounts of antimicrobial agents, in most cases originated from hospitals and farms, include optimization of disinfection procedures and management of wastewater and manure. A policy for preventing mixing of human-originated and animal-originated bacteria with environmental organisms would certainly be advisable (116). However, no recommended method has yet proven sufficiently efficient, safe, and cheap to use on a large scale, particularly in developing countries. Note that antibacterials are not among the products currently listed by the EU Council directive on environmental quality standards in the field of water policy (117).

A second suggestion is to implement measures targeting patients. Since one of the major drivers of bacterial resistance is the accumulation of antibiotic residues in the colonic microbiota (118), the development of colon-targeted companion treatments has been proposed to destroy (119) or inhibit (120) these residues without exerting an impact on the systemic efficacy of antibiotic therapies. However, as promising as these approaches might appear, they have not been tested to prevent the emergence of ESBL-E and still have to prove their efficacy in large-scale clinical trials.

Lastly, the question of decontamination of colonized patients has been raised, mimicking what is done to prevent the dissemination of resistant bacteria and infection in intensive care patients by selective digestive decontamination (121). Although the initial results for carbapenemase carriers appeared promising (122), those obtained subsequently with ESBL-E carriers were disappointing, with short-lived ESBL-E elimination after the end of the procedure (123). Others have tried to use probiotics (124), but this was also a failure. Overall, it seems that far more research is warranted in the field before any practical solution can be proposed. Indeed, there will be a need to clarify the regulatory procedure before envisaging significant developments (125).

However, besides these promising current developments, the simplest hygienic behaviors should not be forgotten. Indeed, in many parts of the world, hand washing remains inadequate (126). Although the effects of promoting hand washing on ESBL-E spread have not been evaluated specifically, its benefits regarding the control of fecally-orally transmitted diseases are unequivocal (127–129). This is why hand washing appears to be a necessary step for the control of ESBL-E in the community. Moreover, since the costs associated with soap supplies are low, hand-washing education should be among public health priorities.

CONCLUSIONS

The main information gained by this review is that the ESBL enzyme pandemic emerged in the community in the early 2000s and has since increased regularly in all regions in a significant manner, sometimes dramatically, with carriage rates exceeding 50% after 2008 in part of Southeast Asia. Differences in the increases in carriage rates were highly significant between Europe, where they are currently around 10%, and less developed regions, where they are higher, explaining why travelers are at risk of becoming colonized while visiting countries abroad. From the beginning, CTX-M alleles accounted for the majority of cases, very often exceeding 90% (Table 1).

The biological characteristics of the colonizing strains may bring some light to bear on why and how resistance has disseminated so well. Although specific clones such as ST131 may play a role in the pandemic (66), the usual lack of clonal relatedness between strains from different carriers suggests that the predominant CTX-M genes are carried by genetic elements that are highly mobile between strains. In addition, CTX-M alleles, which were first found to be different between regions, tend to homogenize. Today, CTX-M-15 ranks first in most regions and is challenging CTX-M-14 in Southeast Asia and CTX-M-2 in South America. This review supports the contention that mobile genetic elements are the cornerstone of the current CTX-M pandemic, as recently reviewed (11). Plasmids have been involved in the intercontinental spread of CTX-M-15 (130), and community outbreaks may also result from strain-to-strain transmission of plasmids. The plausibility of this scenario is also supported by the reported association between CTX-M enzymes and *E. coli* IncF resident plasmids (12, 131), which have the ability to interchange between *E. coli* strains, to which they are particularly well adapted (132). Full sequencing of plasmids should shed further light on this matter in the near future.

This history of CTX-M enzyme dissemination shows parallels with the emergence of TEM-1, a well-known wild-type narrow-spectrum penicillinase which was first isolated in 1965 in Greece (133) and later spread through healthy populations worldwide (134–137). The rapid and wide dissemination of this gene in cattle as well as in food, pets, and environments (138–142) is also paralleled by recent observations made for CTX-M (143). The commu-

nity certainly appears to be the major reservoir of CTX-M-type ESBL (Fig. 3). The presence of this type of enzyme in hospitalized patients is probably only a secondary consequence (144), but it can, however, give rise to subsequent nosocomial outbreaks (103).

A limitation of this analysis is the fact that there was no study for many areas, such as Eastern Europe, Australia, and North America. Also, the question may be posed as to whether the data analyzed are representative of the current trends in ESBL-E epidemiology. Indeed, only studies focusing on community settings were selected; therefore, some important information may have been excluded. In addition, our data analysis may be biased as a result of the diverse methods used by the authors who collected them. Overall, the definition of the healthy community population is not univocal, and medication, chronic diseases, and antibiotic exposure were sometimes considered exclusion criteria. Heterogeneous screening methods (antibiotic agent and concentration used in the selective media) and epidemiological designs (mainly cross-sectional studies, but also case-control studies or cohorts) were used as well. Nonetheless, our analysis probably provides the most relevant conclusions that can be drawn from current literature. They also show that apart from a reduction in antibiotic usage and promotion of hand washing, our means of action are very limited.

Altogether, our results show not only that CTX-M-type ESBL have spread to communities but also that carriage rates are on the rise. This is obviously a major public health concern, particularly in the regions where the rates are very high. The drivers of this catastrophic epidemiology are not fully understood. They may include (i) the genetic material bearing these enzymes, which appears to be extremely well adapted to their bacterial hosts; (ii) the predominance of *E. coli*, an intestinal commensal species widely distributed in both humans and animals, as a bacterial host; (iii) the vast dissemination of CTX-M-type ESBL strains in all kinds of environments; and (iv) the increase in selective pressure due to the multiple uses of extended-spectrum cephalosporins, which are now cheap and widely available as generics. In addition to strong policies to reduce antibiotic misuse in all parts of the world, detailed studies and applied research are urgently needed to determine the best countermeasures which can be implemented.

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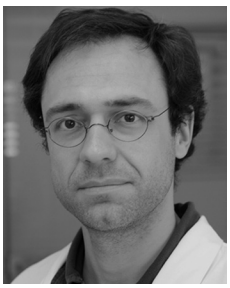

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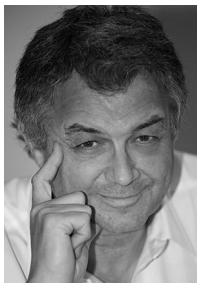
Charles Burdet, M.D., M.P.H., was trained in public health at the Paris 5-René Descartes University, France. He currently specializes in infectious diseases. Since 2011, he has been working at the Bichat-Claude Bernard Hospital (AP-HP, Paris, France), in collaboration with clinicians and microbiologists, with a particular focus on statistical modeling in infectious diseases. His main areas of interest include the pharmacokinetics of antimicrobial agents and the emergence of bacterial resistance. In 2014, he will join the Department of Infectious Diseases at the Bicêtre Hospital, Le Kremlin Bicêtre, where he will work as a fellow.

Continued next page

Elisabeth Chachaty obtained her Pharm.D. at the University of Nancy in 1991 and her Ph.D. at the University of Paris-South in 1993, as a microbiology specialist. Her main fields of research focus on resistance to antibiotics and the deleterious effects of antibiotic treatments on the human intestinal microflora. She is currently Head of the Laboratory of Microbiology at the Institut de Cancérologie Gustave Roussy, Villejuif, France, and specializes in the diagnosis and epidemiology of infections in immunocompromised patients.



Antoine Andremont obtained his M.D. at the University of Tours in 1976 and his Ph.D. at the University of Paris-South in 1986. Initially trained in pediatrics, microbiology, and tropical medicine in France, the United States, and Madagascar, he is currently a Full Professor of Microbiology at the University of Paris 7 Medical School and Head of the Bacteriology Laboratory of Bichat-Claude Bernard University Hospital in Paris (France). He specializes on the impact of antibiotics on the dynamics of bacterial resistance in the intestinal microbiota and has conducted numerous studies in this field in various parts of the world.