Pro Index | Journal of Science in Medicine and Life

Volume: 2 Issue: 11 Year: 2024

ISSN: 2992-9202 | http://journals.proindex.uz

Limitation of Colibactin from *Klebsiella Pneumonia*

Walaa Shakir Mahmood

Baghdad University –College of Science –Biotechnology department, Iraq

Abstract: Klebsiella pneumoniae is the primary pathogen responsible for most cases of meningitis in the community. Nevertheless, the absence of a biologically significant meningitis model for K. pneumoniae has hindered investigations into its pathogenesis mechanism. The highly virulent K1 K. pneumoniae strains, linked to adult meningitis, are predominantly part of a unified clonal complex. Certain strains of K. pneumoniae contain a genetic cluster that is in charge of producing colibactin. Colibactin is a compact molecule with genotoxic properties that is produced through biosynthesis and is governed by genes found on the gene island. In contrast to other highly infectious K. pneumoniae that mainly target the liver, the K1 strains that produce colibactin showed a strong preference for infecting the brain. A meningitis model that is relevant to physiology using K1 K. pneumoniae. Successful induction of acute meningitis was achieved by inoculating K1 K. pneumoniae via orogastric, intranasal, and intravenous routes. In addition to the usual signs of bacterial meningitis, the colibactin-producing K1 K. pneumoniae strain also caused severe DNA damage and individual cell death. Removing the gene that stops the production of colibactin significantly reduced the ability of K. pneumoniae to cause severe illness in the crucial stages of meningitis formation. Colibactin is required, but not the only factor, for the ability of K1 K. pneumoniae to infect the meninges. The bacterial genotoxin colibactin disrupts the eukaryotic cell cycle by inducing double-stranded DNA breaks. It has been associated with bacterially triggered colorectal cancer in individuals. Enterobacteriaceae encodes Colibactin in a 54kb genomic region.

Key points: K.pneumnia-toxin -limitation.

Introduction

Recent research is pinpointing *Klebsiella pneumoniae* as a novel factor in both triggering and progressing gastrointestinal disorders. Initially, *K. pneumoniae* does not inhabit the gut, but it could potentially do so in the future. Nonetheless, the precise timing of gut colonization by *K. pneumoniae* is still unclear, As reported by (1,2), gastrointestinal diseases (GIT) are one of the most common worldwide. Essentially, there are two main types of gastrointestinal disorders: inflammatory bowel diseases (IBD) and cancerous diseases. In developed countries, colorectal cancer (CRC) is the main cause of cancer-related sickness and mortality .In the end, the human gut microbiota is made up of various types of microbes, such as helpful symbionts, neutral bacteria, and harmful pathogens, all playing a role in human well-being and illness. Therapies for colon cancer consist of surgery, chemotherapy (such as FOLFOX, FOLFIRI, etc.), radiotherapy, and immunotherapy(3,4). The abbreviation CRC stands for…

In the last decade, *K. pneumoniae* has become a global threat to human health. Because of the increase in strains that are resistant to multiple drugs, dealing with infections caused by this bacterium has become difficult in healthcare settings. As per (5,6), *K. pneumoniae* strains can be grouped into either "classic" or "hypervirulent" based on their levels of virulence. Most hospital-acquired infections are due to "typical" *K. pneumoniae* strains, which have low virulence and tend to develop resistance to antibiotics such as ESBL or carbapenem. Since the mid-1980s, there has been an acknowledgment of the emergence of very aggressive types of *K. pneumoniae,* particularly

in Taiwan. These strains show strong virulence and cause severe infections obtained in the community, such as pyogenic liver abscess, meningitis, and endophthalmitis . Highly virulent types of K. pneumoniae are frequently recognized as serotypes K1 or K2 out of the 78 capsular serotypes. However, some of the "traditional" *K. pneumoniae* strains are also categorized as K1 or K2. A majority of hypervirulent K1 *K. pneumoniae* strains were found to belong to the CC23 clonal complex in recent studies using a 694-gene core genome MLST scheme (5). This indicates that clonal lineage CC23 has a unique genetic composition that provides it with heightened virulence and fitness. Various variations of a genetic segment housing genes responsible for synthesizing yersiniabactin, colibactin, and microcin E492 were specifically identified in the genome of K1 CC23 highly virulent *K. pneumoniae* strains . Bacterial meningitis is considered one of the most serious brain diseases. A common occurrence of bacterial meningitis in adults is often linked to hyper virulent *K. pneumoniae*, particularly the K1 CC23 strain.

The colibactin genes often occur together with the yersiniabactin biosynthetic determinant. We found out by researching the extent and variety of the colibactin determinant and its connection to the yersiniabactin operon in prokaryotic genomes. primarily unique lineages of colibactin determinant and categorized three primary structural configurations of colibactin – Genomic region of yersiniabactin in Enterobacteriaceae. The colibactin gene cluster shows similarities in evolution but is not exactly the same. trace of the yersiniabactin operon. Both factors could have been obtained multiple times and/or traded. autonomously among enterobacteria through horizontal gene transfer. Integrative and conjugative elements have been of great importance. in the development and variety of structures within the colibactin-yersiniabactin genomic region. In an initial effort to link colibactin expression with specific colibactin determinant lineages We examined colibactin expression of chosen enterobacterial isolates in vitro, using varying bacterial genetic backgrounds. Colibactin production was generally higher and more uniform in the tested *Klebsiella* species and *Citrobacter koseri* strains. higher than the majority of *Escherichia coli* strains examined. Our findings enhance the comprehension of the various forms of colibactin. Determinants, their level of expression, and their potential role in the risk assessment of colibactin-producing enterobacteria.(6)

Colibactin, generated by non-ribosomal synthesis as a combination of peptide andpolyketide...secondary compound found in various bacterial species Family Enterobacteriaceae. The system in charge of creating colibactin. The genetic code is formed by a 54kb polyketide synthase (pks) or clb genome.islet (7) which consists of 19 genes. Most of the island consists of the largest part. consists of a cluster of genes that are either overlapping or located near each other : clbB to clbL and clbN to clbQ, arranged consecutively on the same strandand create coding guidelines for components of the biosynthesis framework. The production of colibactin is improved thanks to the use of a specificcarrier. coded by clbM, and a protein that confers resistance encoded by Limit switch (8,9) is defined as a switch that is activated or deactivated when a certain limit or threshold is reached. Roughly positioned are two additional genes required for the creation of colibactin. The clbR gene, encoding for the biosynthesis of gene Opposite, is located 400 base pairs before clbB in the oppositedirection. Colibactin could potentially interfere with the progression of the eukaryotic cell cycle by forming cross-links.

Genetic instability is caused by DNA breaks resulting in the formation of double-stranded DNA.

Organisms that have cells which have a nucleus (7,10,11) The ability to produce colibact in is available. have been shown to boost the capacity of the disease to cause harm Associated with promoting the development of bacteria involved in colorectal cancer (12,13) as well as linked with beneficial effects. making mention of the host (14,15,16) Colibactins are microscopic compounds that have the ability to cause genetic damage, and their specific structure remains unknown, being produced by the regular gut bacteria found in human intestines. Secondary metabolites are compounds synthesized by a specific gene cluster that was first identified and researched by Oswald et al. in 2006 in an ExPEC strain obtained from neonatal meningitis. Research in epidemiology has shown that colibactin can be produced by disease-causing strains of Enterobacteriaceae found in the intestines, including Klebsiella pneumoniae, Enterobacter

aerogenes, and Citrobacter koseri, as well as in *Pseudovibrio* spp. found in sea sponges (3,4). Bacterial toxin formation involves the enzymes Polyketide synthases (PKSs) and non-ribosomalpeptide synthases (NRPSs). The main production of these extra substances is controlled by the clb A-S genes found in the 54-kilobase genomic pks island, and any change in these genes, except for clbS, results in a decrease or lack of the harmful effect. The importance of this group of genes in colibactin production is demonstrated by clbA, which codes for a PPTase, and clbP, a D-amino peptidase essential for colibactin formation (7). Despite previous research by Brotherton and Balskus, the assembly of colibactin as a prodrug through NRPSPKS biosynthesis machinery with a longer side chain on N-acyl-D-asparagine still lacks full understanding, leaving some mystery surrounding its structure.

Meningitis caused by *K. pneumoniae* is generally a severe condition characterized by multiple septic metastatic lesions in organs such as the liver, eyes, lung, and kidney, and may develop shortly after being admitted to the hospital Studies have shown that mortality rates for *K. pneumoniae* meningitis range from 33.3% to 48.5%. Following treatment, more than 50% of individuals with *K. pneumoniae*-induced meningitis and brain abscess encountered enduring neurological problems . Despite the high mortality rates, there is limited research on the pathogenesis mechanism of *K. pneumoniae* meningitis. *K. pneumoniae* 1084, a very contagious K1 strain, possesses a 208-kb genetic island and is classified under clonal complex CC23 based on phylogenetics. This genetic island, known as KPHPI208 and spanning 208 kilobases, is comprised of eight genetic modules . The original genomic module contains genes that are about 100% similar to the ones present in the pks island of *Escherichia coli* strain IHE3034, linked to infant meningitis. The 54-kilobase pks island contains a non-ribosomal peptide synthetase-polyketide synthase (NRPS-PKS) assembly line, which produces colibactin, a genotoxic metabolite. An ephemeral infection with *E. coli* strains that produce colibactin resulted in DNA damage in host cells in both experimental conditions and living beings . Recent studies on *E. coli* have linked the creation of colibactin to prolonged bacterial presence in the intestine, the development of colorectal tumors, and the initiation of systemic infection in infants.**(16)**

K. pneumoniae 1084 is characterized as a K1 CC23 strain with the pks+ gene and is registered as KPHPI208. A previous study demonstrated that deleting clbA, which produces colibactin via a 4'-phosphopantetheinyl transferase (PPTase), significantly decreased *K. pneumoniae* 1084's capacity to induce DNA harm in both controlled environments and living beings. Although many hypervirulent *K. pneumoniae* strains can lead to invasive infections by colonizing the intestines, their main target organ for infection is the liver. The presence of specific elements from K1 CC23 in *K. pneumoniae* 1084 attracts it to the central nervous system, leading to the development of bacterial meningitis. To comprehend the molecular mechanism, we generated meningitis models utilizing *K. pneumoniae* 1084 that were biologically significant. Through the utilization of orogastric and intranasal techniques for inoculation, *K. pneumoniae* 1084 induced meningitis within a period of 5-7 days, demonstrating the ability of this pks+ K1 CC23 strain to penetrate mucosal defenses. This specific strain of bacteria caused meningitis quickly following intravenous injection because it was resistant to clearance from the blood and able to breach the blood-brain barrier within a day. Analysis of brain tissue samples from mice with *K. pneumoniae* 1084 infection revealed typical signs of acute bacterial meningitis. Moreover, this particular strain, which releases colibactin, induced DNA harm and extensive cell demise in the brain. The full virulence of causing meningitis by *K. pneumoniae* 1084 required the presence of colibactin. The ΔClbA mutant displayed a significant decrease in important disease-causing activities that result in meningitis.

(17,18) suggestion has been put forward. the significant correlation seen between colibactin and The yersiniabactin gene clusters are affected by the colibactin and yersiniabactin biosynthetic pathways interaction, specifically through phosphopantetheinyClbA, which also plays a role in yersiniabactin biosynthesis .The colibactin determinant, known for its high level of conservationhas been noticed in different varieties including the Enterobacteriales group is mostly present in its members belonging to the Enterobacteriaceae family, like *Escherichia coli* Following phylogroup

B2 strains are *K. pneumoniae*. happen in not just individual cases, but also in *Citrobacter koseri* and *K. aerogenes* .Sure, please provide the text that you would like me to paraphrase.

2, 18, and 24 need to be rephrased. Different versions of the colibactin gene cluster that are not as well preserved or are similar in structure have been observed in terms of their characteristics. sourced from the genetic code of a different individual Enterobacterales, a type of Erwinia oleae, along with honey. the bacterium *Frischella perrara* found in bees, and the *alphaproteobacterium Pseudovibrio* found in the ocean (19,20)Due to the restricted similarity in the sequence of the colibactin genes discovered in Enterobacterales, as well as in *F. perrara and Pseudovibrio*, are two analogous polyketide genes. because of their association with mobile genetic elements (MGEs) or situated onIt can be inferred that genes linked to restricted movement may indicate The clb gene cluster could spread via horizontal gene transfer. by means of an ICE-like element The colibactin determinant is frequently associated with a majority of Enterobacteriaceae. ICE exhibits the usual attributes of mobility and transportation. There are no ICE found in the sequence context of the pks island. *Escherichia coli* strains that are part of phylogroup B2. Nevertheless, the pks The island within Escherichia coli can still be moved and passed on by outside influences, which backs up the theory that. Former mobile genetic elements could undergo a homing process that leads tostabilization.after they were incorporated into the chromosomes (21) Study focusing on the prevalence of colibactin genes. So far, mainly focused on *Klebsiella* species or *Escherichia coli*. different encounters and backgrounds. The absence of knowledge in different prokaryoticspeciesregarding the distribution and arrangement of the related MGE struggles to consistently offer additional information about the topic. dissemination and growth of this polyketide compound There are 18 apples on the tree. Previous data suggests that the frequency varied between 5.3

In *Klebsiella*, the percentage was 25.6%, while in *Escherichia* it was 58%, with a variation from 9.5% to 58%. highlighting the specific focus on the pks island ecosystems, as well as research with a broader scope technique resulted in a 14% occurrence of *Klebsiella.* Samples of *Escherichia* bacteria showed a frequency of 9.5%, as reported in references 2 and 29–34. It should be mentioned that, There was a stronger link discovered between the clb genes and health in research.was observed in strains exhibiting increased virulence possibility, with *Klebsiella's* dominance increasing to 78.8% subset and 72.7% for *E. coli* strains associated with colorectal cancer (22, 23]. The genes that produce colibactin are responsible.frequently observed in extremely combative and refractory to numerous medicationsSamples of *K. pneumoniae* (24,25), (26). Enterobacteriaceae members such as *E. coli* and *K. pneumoniae* with pks were found in different clinical situations like newborn meningitis, gut flora in humans and animals, patients with urinary tract infections, and cases of septicemia. Furthermore, *E. coli* that possess pks have been discovered in colorectal cancer (CRC) and could potentially play a role in advancing human CRC (27) It was found that deleting clbA greatly decreases *K. pneumoniae* strain 1084's ability to damage DNA when it carries the pks cluster, in both laboratory and living organism environments.

However, studies have shown that clbP can reduce the harmful effects of this toxin in a lab environment and notably decrease the amount of tumors in a live organism (28) This research aimed to analyze the prevalence of specific genes responsible for producing colibactin among patients in Iraq who are infected with Enterobacteriaceae. Furthermore, evaluated the potential of the isolates with pks genes to induce negative impacts on the HeLa cell line via cytotoxicity and genetic harm in vivo. Method: Isolating and Identifying Bacteria Collection of diverse clinical samples (stool, urine, blood, and wound swabs) from various patients was done to avoid duplication for the purpose of isolating Enterobacteriaceae(29,30,31,32)

Conclusion

K. pneumoniae 1084 belongs to the K1 CC23 strain and produces colibactin. Unlike other typical K1 CC23 *K. pneumoniae* strains that cause liver abscesses, 1084 has a gene cluster identical to the island responsible for colibactin production. Just like in *E. coli*, removing clbA stopped the creation of colibactin and weakened the harmful effects of *K. pneumoniae* 1084 on mammalian cells.

Besides this toxicity, *K. pneumoniae* 1084 also showed a preference for infecting the meninges in adult BALB/c mice. Following the decrease in gut microbiota due to the introduction of streptomycin into the drinking water, the orally introduced *K. pneumoniae* 1084S (a strain resistant to streptomycin; 10^9 CFU) successfully colonized the intestines, spread quickly throughout the body, and caused meningitis in every mouse that was inoculated within a week. *K. pneumoniae* 1084 did not show a preference for the meninges like *K. pneumoniae* CG43, which we utilized in the liver abscess model in BALB/c mice. CG43 colonized the intestines and could spread outside of the intestines to cause systemic infections, but did not often cause meningitis simultaneously.CG43 is a strain of K2 ST86 with heightened virulence but lacking colibactin. We then investigated how much colibactin is involved in the meningeal tropism of *K. pneumoniae* 1084. While ΔClbA replicated similarly to strain 1084S in the intestines, its ability to adhere to the mucosa of both small and large intestines was greatly impacted by the absence of clbA. This finding supported the idea that the presence of colibactin is linked to the ability of *E. coli* strains from phylogenetic group B2 to sustain long-term colonization in the intestines.

Colonization of the intestine is necessary for *K. pneumoniae* to cause systemic infections. The removal of clbA impacted *K. pneumoniae's* ability to colonize the intestinal lining and move into other tissues outside the intestine. This outcome indicated that colibactin may play a part in the intestinal movement of *K. pneumoniae* 1084S. The presence of colibactin did not lead to intestinal damage. However, the 1084S group showed an increase in submucosal space and slight hyperemia in the small intestines compared to the control group. This indicates that colibactin production could potentially trigger inflammation in the intestinal mucosa. Comparative analysis of RNA-seq in the mucosa showed that certain genes related to inflammation were notably increased in mice inoculated with *K. pneumoniae* 1084S compared to the ΔClbA group. CCL17, CCL8, and MMP9 were notably upregulated in response to the colibactin-producing *K. pneumoniae.*

ClbA, a phosphopantetheinyl transferase (PPTase) of 4', is essential for the production of colibactin. In *E. coli*, ClbA is additionally responsible for the synthesis of PPTase-dependent siderophores. Nevertheless, the absence of clbA did not impact the siderophore production in *K. pneumoniae* 1084, as shown by SideroTec test with average siderophore amounts of 82 and 85 μg/ml in 1084S. The reason why there is no effect on siderophore production in *K. pneumoniae* 1084 could be due to the fact that aerobactin is the main siderophore produced by this strain. The iucABCD operon encodes its biosynthesis and does not rely on PPTase. Deleting iucA reduced aerobactin production and weakened *K. pneumoniae* virulence in animal models. Salmochelin, enterobactin, and yersiniabactin are not necessary for the growth and survival of hypervirulent *K. pneumoniae* strains in laboratory conditions and in living organisms.

Various factors like chronic inflammation, diet, and antibiotics can alter microbiome composition. The exact mechanisms remain unknown. Studies show a connection between cancer rates and the human microbiome. In the future, gut microbiota may serve as a marker to distinguish between healthy and tumor patients. Additionally, prebiotics and probiotics could be used for preventive care to restore a healthy gut microbiota and halt cancer progression, or be given alongside chemotherapy for oncology patients. We outlined the occurrence of pks positive E. coli and pks positive *K. pneumoniae* in samples from patients with CRC, and explained the impact of pks positive bacteria on epithelial CRC cells both in laboratory settings and in living organisms. It appears that pks-positive bacteria have the ability to cause mutations in CRC driver genes, making pks a potential indicator of CRC development and treatment.

References:-

1. Sperber,A.D..et al.2021. Worldwide prevalence and burden of functional gastrointestinal Gastroenterology. 2021 Jan;160(1):99-114
2. Eyvazi, S., Vostakolaei, M.A., Dilmaghani, A., Borumandi, O., Hejazi, M.S., Kahroba, H. Tarhriz, V., 2020. The oncogenic roles of bacterial infections in development of cancer. Microb. Pathog. 141, 104019

3. Lin, C., Cai, X., Zhang, J., Wang, W., Sheng, Q., Hua, H., Zhou, X., 2019. Role of gut microbiota in the development and treatment of colorectal cancer. Digestion 100,72-78.
4. Bialek-Davenet S., Criscuolo A., Ailloud F., Passet V., Jones L., Delannoy-Vieillard A. S., et al.. 2014. Genomic definition of hypervirulent and multidrug-resistant Klebsiella pneumoniae clonal groups. Emer. Infect. Dis. 20, 1812–1820.
5. Struve C., Roe C. C., Stegger M., Stahlhut S. G., Hansen D. S., Engelthaler D. M., et al.. 2015. Mapping the evolution of hypervirulent Klebsiella pneumoniae. MBio 6, e00630.
6. Shon, A. S., Bajwa, R. P., Russo T. A. 2013. Hypervirulent (hypermucoviscous) Klebsiella pneumoniae: a new and dangerous breed. Virulence 4, 107–118
7. Nougayrède, J-P., Homburg, S., Taieb, F., Boury, M., Brzuszkiewicz, E.*et al*. *2006Escherichia coli* induces DNA double-strand breaks in eukaryotic cells. Science;313:848–851.
8. Putze, J., Hennequin, C., Nougayrède, J-P., Zhang, W., Homburg, S. *et al.* 2009. Genetic structure and distribution of the colibactin genomic island among members of the family Enterobacteriaceae. Infect Immun; 77:4696–4703.
9. Xue, M., Kim, C.S., Healy, A.R., Wernke, K.M., Wang, Z. *et al*. 2019.Structure elucidation of Colibactin and its DNA cross-links. Science 365:6457.
10. Homburg, S., Oswald, E,, Hacker, J., Dobrindt, U. 2007.Expression analysis of the colibactin gene cluster coding for a novel polyketide in Escherichia coli. FEMS Microbiol Lett 275:255–262.
11. Wallenstein, A., Rehm, N., Brinkmann, M., Selle, M., Bossuet-Greif, N. *et al.* 2020.ClbR is the key transcriptional activator of colibactin gene expression in Escherichia coli. mSphere; 5:e00591-00520.
12. Healy, A.R., Wernke, K.M., Kim, C.S., Lees, N.R., Crawford, J.M. *et al.* 2019.Synthesis and reactivity of Precolibactin 886. Nat Chem 11:890–898.
13. Li, Z-R., Li, J., Gu, J-P., Lai, J.Y.H., Duggan, B.M. *et al*. 2016.Divergent biosynthesis yields a cytotoxic aminomalonate-containing precolibactin. Nat Chem Biol;12:773–775.
14. Nougayrède, J-P., Homburg, S., Taieb, F., Boury, M., Brzuszkiewicz, E. *et al*. 2006.Escherichia coli induces DNA double-strand breaks in eukaryotic cells. Science 313:848–851.
15. Cuevas-Ramos, G.,Petit, C.R.,Marcq, I.,Boury, M.,Oswald, E,*et al*.2010.Escherichia coli induces dna damage in vivo and triggers genomic instability in mammalian cells.Proc Natl Acad Sci U S A;107:11537–11542
16. Bossuet-Greif, N., Vignard, J., Taieb, F., Mirey, G., Dubois, D. *et al*. 2018.The colibactin genotoxin generates DNA interstrand cross-links in infected cells. mBio 9:e02317–e02393.
17. Buc, E., Dubois, D., Sauvanet, P., Raisch, J., Delmas, J. *et al*.2013. High prevalence of mucosa-associated E. coli producing cyclomodulin and genotoxin in colon cancer. PLoS One 8.
18. Pleguezuelos-Manzano, C., Puschhof, J., Rosendahl, Huber, A., van Hoeck, A., Wood, H.M. *et al*. 2020.Mutational signature in colorectal cancer caused by genotoxic pks+ E. Coli. Nature 580:269–273.
19. Faïs, T., Delmas, J., Barnich, N., Bonnet, R., Dalmasso, G. 2018.Colibactin: more than a new bacterial toxin. Toxins (Basel) 10.
20. Wilson, M.R., Jiang, Y., Villalta, P.W., Stornetta, A., Boudreau, P.D. *et al*. 2019.The human gut bacterial genotoxin colibactin alkylates DNA. Science 363:eaar7785.
21. Brzuszkiewicz, E., Brüggemann, H., Liesegang, H., Emmerth, M., Olschläger, T. *et al.* 2006. How to become a uropathogen: Comparative genomic analysis of extraintestinal pathogenic Escherichia coli strains. Proc Natl Acad Sci U S A 103:12879–12884.

22. Bellanger, X., Payot, S., Leblond-Bourget, N., Guedon, G. 2014.Conjugative and mobilizable genomic islands in bacteria: evolution and diversity. FEMS Microbiol Rev 38:720–760.

23. Engel, P., Vizcaino, M.I., Crawford, J.M. 2015.Gut symbionts from distinct hosts exhibit genotoxic activity via divergent colibactin biosynthesis pathways. Appl Environ Microbiol 81:1502–1512.

24. Moretti, C., Hosni, T., Vandemeulebroecke, K., Brady, C., De Vos, P.*et al*.2011. Erwinia oleae sp. nov., isolated from olive knots caused by Pseudomonas savastanoi pv. savastanoi. Int J Syst Evol Microbiol 61:2745–2752.

25. Schneider, G., Dobrindt, U., Middendorf, B., Hochhut, B., Szijártó, V. *et al.* 2011. Mobilisation and remobilisation of a large archetypal pathogenicity island of uropathogenic Escherichia coli in vitro support the role of conjugation for horizontal transfer of genomic islands. BMC Microbiol 11:210.

26. Chen, Y-T., Lai, Y-C., Tan, M-C., Hsieh, L-Y., Wang, J-T.*et al*. 2017.Prevalence and characteristics of pks genotoxin gene cluster-positive clinical Klebsiella pneumoniae isolates in Taiwan. Sci Rep 7:43120.

27. Yoshikawa, Y.,Tsunematsu, Y.,Matsuzaki, N.,Hirayama, Y.,Higashiguchi, F. *et al*. 2020. Characterization of colibactin-producing Escherichia coli isolated from Japanese patients with colorectal cancer. Jpn J Infect Dis 73:437–442.

28. Lam, M.M.C., Wick, R.R., Wyres, K.L., Gorrie, C.L., Judd, L.M. *et al*. 2018.Geneticdiversity, mobilisation and spread of the yersiniabactin-encoding mobile element ICEKp in Klebsiella pneumoniae populations. Microb Genom;4

29. Shen, P., Berglund, B., Chen, Y., Zhou, Y., Xiao, T. *et al*. 2020.Hypervirulence markers among non-ST11 strains of carbapenem- and multidrugresistant Klebsiella pneumoniae isolated from patients with bloodstream infections. Front Microbiol 11:1199.

30. Bossuet-Greif, N., Vignard, J., Taieb, F., Mirey, G., Dubois, D., Petit, C. *et al*. 2018.The colibactin genotoxin generates DNA inter-strand crosslinks in infected cells. mBio. 9

31. Raisch, J., Buc, E., Bonnet, M., Sauvanet, P., Vazeille, E., de Vallee. *et al*.2014. Colon cancer-associated B2 Escherichia coli colonize gut mucosa and promote cell proliferation. World J. Gastroenterol. 20: 6560-6572.

32. Faïs, T., Cougnoux, A., Dalmasso, G., Laurent, F., Delmas, J., Bonnet, R. 2016.Antibiotic activity of Escherichia coli against multiresistant Staphylococcus aureus. Antimicrob. Agents Chemother. 16: 6986-6988.