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## What's new in the anti-*Pseudomonas aeruginosa* clinical development pipeline since the 2017 WHO alert?

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### 13 **ABSTRACT**

14 The spread of antibiotic-resistant bacteria poses a substantial threat to morbidity and mortality  
15 worldwide. Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) are considered “critical-priority”  
16 bacteria by the World Health Organization (WHO) since 2017 taking into account criteria such as  
17 patient mortality, global burden disease and worldwide trend of multi-drug resistance (MDR). Indeed  
18 *P. aeruginosa* can be particularly difficult to eliminate from patients due to its combinatorial antibiotic  
19 resistance, multifactorial virulence and ability to over-adapt in a dynamic way. Research is active but  
20 the course to a validated efficacy of a new treatment is still long and uncertain. What's new in the anti-  
21 *P. aeruginosa* clinical development pipeline since the 2017 WHO alert? This review focuses on new  
22 solutions for *P. aeruginosa* infections that are in active clinical development, i.e., currently being tested  
23 in humans and may be approved for patients in the coming years. Among 18 drugs of interest in  
24 December 2021 anti-*P. aeruginosa* development pipeline described here, only one new combination  
25 of  $\beta$ -lactam/ $\beta$ -lactamase inhibitor is in phase III trial. Derivatives of existing antibiotics considered as  
26 “traditional agents” are over-represented. Diverse “non-traditional agents” including bacteriophages,  
27 iron mimetic/chelator and anti-virulence factors are significantly represented but unfortunately still in  
28 early clinical stages. Despite decade of efforts, there is no vaccine currently in clinical development to  
29 prevent *P. aeruginosa* infections. Studying pipeline anti-*P. aeruginosa* since 2017 up to now, shows  
30 how to provide a new treatment for patients can be a difficult task. Given the process duration, the  
31 clinical pipeline remains unsatisfactory leading best case to the approval of new antibacterial drugs  
32 that treat CRPA in several years. Beyond investment needed to build a robust pipeline, the Community  
33 needs to reinvent medicine with new strategies of development to avoid the disaster. Among “non-  
34 traditional agents”, anti-virulence strategy may have the potential through novel and non-killing modes  
35 of action to reduce the selective pressure responsible of MDR.

36 **Keywords:** *Pseudomonas aeruginosa*, multi-drug resistance, development pipeline, vaccine,  
37 immunotherapy, antibiotics, phage therapy, anti-virulence strategy.

## 38 INTRODUCTION

39 As a worldwide public health threat, the World Health Organization (WHO) established a list of  
40 antibiotic-resistant bacteria in 2017 (Tacconelli et al., 2018). The aim was to prioritize and stimulate  
41 research and development strategies of new active drugs. Among relevant criteria such as patient  
42 mortality prevalence, health-care burden and trend of resistance worldwide, carbapenem-resistant  
43 *Pseudomonas aeruginosa* (CRPA) were considered “critical-priority” bacteria (Tacconelli et al., 2018).  
44 Indeed, Carbapenem antibiotics are reserved for the treatment of multi-drug resistant (MDR) bacterial  
45 infections and when bacteria develop resistance to them, treatment options become extremely limited.

46 *P. aeruginosa* is an opportunistic pathogen responsible for both severe acute and chronic infections,  
47 and is a significant cause of healthcare-associated infections, particularly in critically ill and  
48 immunocompromised patients (**Figure 1**). Since its first description in wound infections (Gessard,  
49 1882), *P. aeruginosa* is now a well-known pathogen. Pathogenesis of *P. aeruginosa* is mediated by an  
50 arsenal of virulence factors: motility, adherence to biotic and abiotic surfaces, secreted toxins also  
51 called effectors that are released in the environment or injected into host cells or other bacteria (**Figure**  
52 **2**). These effectors are able to modulate or disrupt host cells signaling pathways, target extracellular  
53 matrix, induce tissue damage and shape the local microbiome by competition (**Figure 2**). The ability  
54 of *P. aeruginosa* to form a biofilm is also a key factor that increases drug resistance, escape from host  
55 defense and is responsible for colony tolerance to disinfectants on medical devices (Jurado-Martín et  
56 al., 2021; Pang et al., 2019; Mulcahy et al., 2014). As all these factors contribute to pathogenicity by  
57 complementary actions, *P. aeruginosa* is characterized by a combinatorial multifactorial virulence.  
58 Moreover, multiple mechanisms of antibiotic resistance have been identified, including intrinsic  
59 membrane permeability, drug efflux systems, production of antibiotic-inactivating enzymes and loss  
60 of porin function (Pang et al., 2019). Finally, the plasticity of its (i) virulence factor gene expression,  
61 (ii) antibiotic resistance and (iii) metabolism in response to selective pressure is one of the most  
62 challenging feature of *P. aeruginosa* allowing the transition from acute to chronic infections. Acute  
63 infections are mainly associated with planktonic life style, while biofilm plays a major role in persistent  
64 infections. This remarkable ability of over-adaptation in a dynamic way allows this pathogen to escape  
65 immune system and become multi drug resistant or extensively drug resistant (XDR). Once a chronic  
66 infection in the patient is established, *P. aeruginosa* is really difficult to treat.

67 To meet this major treatment issue, research is active with a variety of approaches ranging from  
68 disarming the pathogen with an anti-virulence strategy to eliminating it. In parallel with the growing  
69 knowledge of the molecular mechanisms of *P. aeruginosa*-host interaction, the number of potential  
70 therapeutic targets is increasing. However, the path to validate efficacy of a new drug in Human is long  
71 and uncertain. Two antibacterial tracks of development are followed and consist in “traditional agents”  
72 (small molecule directly targeting the bacterium for a bacteriostatic or bactericidal action) and new  
73 therapeutics called “non-traditional” (large molecule and/or not acting by directly targeting bacterial  
74 components essential for bacterial growth). Characterized by new, non-bactericidal, and generally  
75 species-specific modes of action, the paradigm is that non-traditional agents are less likely to generate  
76 the dreaded resistance (Tse et al., 2017). Indeed a non-killing agent reduce the selective pressure and  
77 its specificity avoid cross-resistance potentially induced by horizontal genes transfer (Tse et al., 2017).  
78 This review focuses on new solutions for *P. aeruginosa* infections that are in active clinical  
79 development, i.e., currently being tested in humans and may be approved for patients in the coming  
80 years. A literature search was performed in a context of need to address clearly the question: what’s  
81 new in the anti-*P. aeruginosa* clinical development pipeline since the 2017 WHO alert?  
82

## 83 RATIONALE OF THIS REVIEW AND METHODOLOGY OF DATA SEARCH

84 With more than 74,000 articles published in PubMed® in December 2021, knowledge about *P.*  
 85 *aeruginosa* is growing in the fields of its virulence, antibiotic resistance, lifestyle, metabolism, clinical  
 86 manifestations, clinical or observational studies, health and economic burden, among others. Numerous  
 87 articles or reviews detail the potential new targets from basic research, the emerging new candidate  
 88 therapies in early phase, or the pipeline of antibacterial molecules in preclinical and clinical testing and  
 89 the hope that comes with it (Burrows, 2018; Tümmler, 2019; WHO, 2019; Theuretzbacher et al., 2020;  
 90 WHO, 2021; Yaeger et al., 2021). It is difficult to find one's way through all this data, which is often  
 91 mixed and rarely dedicated to *P. aeruginosa*. It is important to keep in mind that before proof of concept  
 92 in a phase II study, no efficacy is proven in patients. Efficacy-safety balance evaluation in *P. aeruginosa*  
 93 infected patients is an unavoidable milestone. To dedicate this review only to anti-*P. aeruginosa*  
 94 treatments in clinical development, a literature search was conducted with a specific strategy in the  
 95 PubMed® database between January 2017 and December 2021. The following criteria were used: (i)  
 96 keywords related to development (antibacterial pipeline, antibiotic pipeline, clinical development) and  
 97 treatment (drug, antibiotic, therapy), (ii) selection of phase I to III clinical trials, and (iii) exclusion of  
 98 research data or preclinical targets (**Figure 3**). Clinical trial registries and websites of companies or  
 99 organizations with a special interest in the field were consulted to verify or supplement the data (**Figure**  
 100 **3**).

## 101 VACCINES: A PROPHYLACTIC STRATEGY FOR HIGH-RISKS PATIENTS

102 A vaccine against *P. aeruginosa* for at-risk patients (i.e., those older than 65 years, those with cystic  
 103 fibrosis (CF), bronchiectasis, or chronic obstructive pulmonary disease) could reduce the prevalence  
 104 of infections, the overall burden disease, and the use of antibiotic treatment. Therefore, although formal  
 105 data are lacking, the vaccine, by limiting the use of antibiotics and thus reducing selection pressure on  
 106 pathogens, has a significant indirect impact on the emergence of antibiotic resistance (Micoli et al.,  
 107 2021; López-Siles et al., 2021). An important challenge for obtaining a good vaccine is the  
 108 identification of ideal antigens, i.e. antigens accessible or presented to the immune system, adequately  
 109 immunogenic and highly conserved across all serotypes (Sainz-Mejías et al., 2020), regardless of the  
 110 stage or location of the infection. Antigen variability, plasticity of virulence factor expression during  
 111 acute to chronic infection described earlier in the introduction, and bacterial localization (the mucosal  
 112 immune response is compromised in dehydrated and sticky mucus in lungs of CF patients) are a  
 113 challenge. In addition, it is also necessary to find a safe but immunogenic vector and antigen  
 114 formulation (with or without adjuvant), allowing mucosal vaccination, intracellular and extracellular  
 115 delivery of antigens to achieve specific cellular and humoral immunity, as well as long-term immunity.  
 116 Finally, the choice of the target pathology is also very important: bacteremia, chronic lung infection,  
 117 keratitis, urinary tract or skin infection for the clinical trial.

118 Despite active research for a *P. aeruginosa* vaccine during over half a century, no vaccine has yet been  
 119 approved (Sainz-Mejías et al., 2020; López-Siles et al., 2021; Micoli et al., 2021). Several antigens  
 120 (lipopolysaccharide LPS, alginate, flagellum, type 4 pili, outer membrane proteins OMPs, type 3  
 121 secretion systems T3SS , T2SS effectors, autoinducers, iron-uptake proteins) have been targeted in  
 122 clinical development, but to date only three vaccines reached the phase III trials (Rello et al., 2017).  
 123 The investigational vaccine IC43, a recombinant OMPs (OprF porin/OprI lipoprotein)-based vaccine,  
 124 appeared to be the last promising based on the favorable safety and immunogenicity profile from phase  
 125 II study (Adlbrecht et al., 2020).

126 **But what's new in the clinical development pipeline since the 2017 WHO alert?**

127 Results from a phase II/III, multicenter, randomized, placebo-controlled, double-blinded confirmatory  
 128 study of IC43 vaccine against *P. aeruginosa* were published in 2020 (Adlbrecht et al., 2020). 799  
 129 patients requiring mechanical ventilation received the vaccine at the time of admission to the intensive  
 130 care unit (ICU). Although the study confirmed the safety profile and immunogenicity, the primary  
 131 endpoint was not met with the IC43 vaccine providing no clinical benefit over placebo in terms of  
 132 overall mortality (29.2% versus 27.7% in the IC43 and placebo groups, respectively, at day 28;  $p=0.67$ )  
 133 (Adlbrecht et al., 2020). The authors suggest that prevention of *P. aeruginosa* infection with a vaccine  
 134 at the time of ICU admission may be too late. Indeed, in general, the humoral immune response is  
 135 obtained about 2 to 3 weeks after the primary injection of the vaccine, which does not allow time to  
 136 obtain a significant effect. Moreover, efficacy of the humoral response could be affected in some  
 137 bacterial infections that are not systemic. An impact on mortality is also very difficult to demonstrate  
 138 in critically ill patients, so another primary endpoint such as *P. aeruginosa*-related events would have  
 139 been a better option. Nevertheless, this study demonstrated the feasibility of vaccinating a large cohort  
 140 of ventilated patients in ICU and inducing a specific immune response (Adlbrecht et al., 2020).

141 Based on the literature search (Sainz-Mejías et al., 2020; Rello et al., 2017; Adlbrecht et al., 2020;  
 142 Merakou et al., 2018; Bianconi et al., 2019), consultation of the clinical trials registry  
 143 (ClinicalTrials.gov., 2021), and probably due to the recommendation published in the Cochrane  
 144 Database of Systematic Reviews (Johansen and Gøtzsche, 2015), no vaccine is currently in clinical  
 145 development (**Figure 4A**). An effective vaccine should be able to induce an humoral immune response  
 146 capable of both mediating opsonophagocytic killing by phagocytic cells and neutralizing *P. aeruginosa*  
 147 virulence factors (Sainz-Mejías et al., 2020). Advances have been made in understanding the  
 148 interaction between *P. aeruginosa* and its host and the key role of Th1 and Th17 host immune responses  
 149 are well established and a cellular immune response mediated by Th17 cells (Sainz-Mejías et al., 2020).  
 150 A deeper understanding of these mechanisms at each potential site and stage of infection would  
 151 facilitate future vaccine development. A novel approach such as reverse vaccinology combined with  
 152 genomic technologies has recently been described in *P. aeruginosa*, identifying potentially surface-  
 153 exposed immunogenic proteins relevant in pathogenesis (Bianconi et al., 2019). The use of outer  
 154 membrane vesicles, because carrying many surface antigens which can serve as targets, also represent  
 155 a promising approach for vaccine development (Antonelli et al., 2021).

## 156 **ANTIBODIES: AN IMMEDIATE PASSIVE IMMUNIZATION TO TREAT OR PREVENT** 157 **INFECTION**

158 The vaccination (or active immunotherapy) strategy has various limitations, particularly for  
 159 immunocompromised patients who may not be able to induce an appropriate immune response.  
 160 Moreover, the immediate need for protection may not be met, including the time required for the  
 161 development of an adequate immune response after vaccination, as discussed above (Adlbrecht et al.,  
 162 2020). The uncommon mucus produced in the CF-lung can also be a barrier to the systemic and specific  
 163 immune response against *P. aeruginosa* that colonize the lower airways. Nevertheless, antibodies  
 164 represent an effective and specific line of defense of the immune system. Passive immunotherapy with  
 165 antibacterial monoclonal antibodies (mAbs) is therefore an alternative therapy against *P. aeruginosa*  
 166 that could be interesting in certain clinical situations. Indeed, mAbs target specific surface antigens  
 167 that are not usually the targets of antibiotics and are thus active against MDR bacteria. Antibacterial  
 168 strategies are developed by mAbs binding to bacterial surface antigens, inducing opsonophagocytic  
 169 killing by the host immune system or by binding to a virulence factor, such as toxin, and thus  
 170 neutralizing it (Lakemeyer et al. 2018). To date, no mAbs against *P. aeruginosa* have been approved.

171 Among the latest anti-*P. aeruginosa* mAbs, AR101 and AR105 have been developed as adjuvant  
 172 strategy to antibiotics. While AR101 targets the LPS serotype O11 surface O-antigen, AR105 targets

173 alginate, a polysaccharide required for biofilm formation (Zurawski et al., 2020; Lu et al., 2011). A  
 174 phase IIa trial evaluating AR101 was completed in 2009 for hospital acquired pneumonia, showing  
 175 promising results in clinical cure and survival rates (NCT00851435). A phase II trial testing the  
 176 efficacy, safety and pharmacokinetic of AR105 in addition to standard-of-care (SOC) antibiotics for  
 177 pneumonia cause by *P. aeruginosa* was started in 2017 (NCT03027609). MEDI3902, a bispecific  
 178 mAb, is able to recognize two different targets of *P. aeruginosa*, each containing a distinct epitope: the  
 179 T3SS needle-tip protein PcrV, involved in host cell cytotoxicity and the surface exopolysaccharide Psl,  
 180 involved in epithelial attachment and biofilm formation (**Figure 2**; Sato et al., 2011; Ryder et al.,  
 181 2007). Designated as a Fast track drug from Food and Drug Administration (FDA), MEDI3902 is  
 182 under development for the prevention of healthcare-acquired *P. aeruginosa* pneumonia in high-risk  
 183 patients<sup>1</sup>. PsAer-IgY (egg yolk immunoglobulin), an avian polyclonal anti-*P. aeruginosa* antibody, has  
 184 entered in a phase III trial to test its efficacy in preventing recurrence of *P. aeruginosa* infection in CF  
 185 patients (Thomsen et al., 2016).

### 186 **But what's new in the clinical development pipeline since the 2017 WHO alert?**

187 Currently in clinical development in China, the future of AR101 is unclear. Being specific to just one  
 188 set of *P. aeruginosa* strains, AR101 mAbs may have limited value in contrast to MEDI3902 directed  
 189 against independent and highly conserved target serotypes among clinical isolates (Tabor et al., 2018).  
 190 In 2019, the developers reported that AR105 was unable to demonstrate superiority over SOC for  
 191 clinical cure of *P. aeruginosa* pneumonia in phase II trial<sup>2</sup>; no further development resources were  
 192 allocated to AR-105. In 2018, several years after the completion of the phase II study in CF patients  
 193 infected with *P. aeruginosa*, results of KB001A were finally published (VanDevanter and Chmiel.,  
 194 2018). KB001A is a monospecific PEGylated anti-PcrV mAb. Because no statistical difference was  
 195 observed in time to antibiotic use compared to placebo, the primary endpoint was unfortunately not  
 196 met. According to the authors, the low levels of T3SS secretion activity of *P. aeruginosa* isolates from  
 197 CF patients may be an explanation for the lack of efficacy observed with KB001A in this study  
 198 (VanDevanter and Chmiel., 2018).

199  
 200 Early use in healthier patients may be effective in reducing the inflammatory effect responsible for  
 201 lung disease progression (VanDevanter and Chmiel., 2018). Published in 2019, results from the phase  
 202 I study of MEDI3902 in healthy subjects (Ali et al., 2019), supported further evaluation in phase II  
 203 proof-of-concept study in mechanically ventilated ICU patients at high risk for *P. aeruginosa*  
 204 pneumonia. Even when bi-specific, MEDI3902 did not achieve the primary efficacy endpoint of  
 205 reducing *P. aeruginosa* pneumonia (Chastre et al., 2020). Nevertheless, positive exploratory results  
 206 were observed in subjects with lower levels of baseline inflammatory biomarkers, a subpopulation that  
 207 could be tested to benefit from MEDI3902 (Chastre et al., 2020). While PsAer-IgY was safe in the the  
 208 population studied, efficacy could not be demonstrated with the trial design used, as stated in the final  
 209 report (EU Clinical Trial register, 2018). The time to first recurrence of *P. aeruginosa* in patient sputum  
 210 was not significantly different between active treatment and placebo. One explanation for this result  
 211 could be that the non-specific IgY used as a comparator is also effective in postponing infection but in  
 212 a nonspecific way (EU Clinical Trial register, 2018). The low efficacy could also be due to use  
 213 antibodies from another specie in humans responsible of neutralizing anti-IgY antibodies production.  
 214 TRL1068, a human mAb targeting DNA Binding protein II (DNABII) is a promising new agent in

215 <sup>1</sup>AstraZeneca website: <https://www.astrazeneca.com/media-centre/press-releases/2014/medimmune-fda-medi3902-nosocomial-pneumonia-prevention-23092014.html#modal-historic-confirmation> [Accessed December 2021]

216 <sup>2</sup>Aridis Pharmaceuticals website: <https://investors.aridispharma.com/2019-09-03-Aridis-Pharmaceuticals-Reports-Phase-2-Clinical-Trial-Results-of-AR-105-for-the-Treatment-of-Ventilator-Associated-Pneumonia-Caused-by-Pseudomonas-Aeruginosa> [Accessed December 2021]

217 <sup>3</sup>Trellis bioscience website: [www.trellisbio.com/pipeline/bacteria.html](http://www.trellisbio.com/pipeline/bacteria.html) [Accessed December 2021]

219 the antibody potentially effective against biofilm produced by a wide range of clinically relevant  
 220 pathogens, including 10 of the 12 WHO priority pathogens<sup>3</sup>. Nevertheless, this efficacy could be low  
 221 with early isolates that does not produce biofilm or are lower producers.

## 222 POLYMYXIN DERIVATIVES: A NEW “OLD” CLASS OF ANTIBIOTICS

223 Almost 60 years after their clinical approval, polymyxins remain a class of antibiotic available for  
 224 many MDR Gram-negative bacteria, but used as last line therapeutic option due to their potential  
 225 human nephro- and neurotoxicity (Li et al., 2019). Polymyxins are small cyclic cationic lipopeptides,  
 226 interacting with the anionic lipid A component of LPS, in the outer membrane of Gram-negative  
 227 bacteria, leading to cytoplasmic membrane disruption and bacterial cytotoxicity (Li et al., 2019). Their  
 228 clinical use has restarted in recent years with polymyxin B and polymyxin E (colistin). Based on  
 229 structure-activity-toxicity relationships, many efforts have been made to modify the original  
 230 polymyxins and improve their safety profile. SPR741 is a polymyxin B derivative with less  
 231 nephrotoxicity. SPR741 has no direct antibacterial activity but potentiates the efficacy of co-  
 232 administered antibiotics (French et al., 2020), which alone would not have access to their intracellular  
 233 targets (Corbett et al., 2017). SPR741 completed a phase I clinical trial in 2017 (Eckburg et al., 2019).

### 234 But what’s new in the clinical development pipeline since the 2017 WHO alert?

235 SPR741, combined with 3 different wide spectrum  $\beta$ -lactam antibiotics (ceftazidime,  
 236 piperacillin/tazobactam, and aztreonam), showed favorable tolerability and PK profiles in a phase Ib  
 237 study (Eckburg et al., 2019). The most effective combinations of such a “potentiator” strategy are not  
 238 known yet, especially in non-healthy patient (Theuretzbacher et al., 2020). The clinical program for  
 239 SPR741 have been halted by the developers in 2020 before phase II in favor of the potentially more  
 240 promising SPR206 molecule (WHO, 2021). This kind of strategic choice is also a reality of clinical  
 241 development, explaining the dynamic change in the pipeline of molecules. SPR206 is another  
 242 polymyxin B derivative, designed for use alone, and has shown antibiotic activity against MDR Gram-  
 243 negative pathogens and XDR bacterial strains, including CRPA, in preclinical studies. It has thus a  
 244 potential broad-spectrum of activity (Brown et al., 2019). Data from a phase I clinical trial were  
 245 recently published with no evidence of nephrotoxicity and supporting further development of SPR206  
 246 (Bruss et al., 2021). Two additional Phase I trials (**Figure 4B**) were also completed in December  
 247 2021: a bronchoalveolar lavage clinical trial assessing SPR206 penetration into the lungs, and a renal  
 248 failure study. How polymyxin resistance and cross-resistance to other classes might develop over time  
 249 is not known. The benefit of SPR206 on polymyxin-resistant strains must be demonstrated and lower  
 250 toxicity must be shown in patients (Theuretzbacher et al., 2020). Nevertheless, the FDA has granted  
 251 SPR206 Qualified Infectious Disease Product (QIDP) designation for the treatment of complicated  
 252 urinary tract infections (cUTI), hospital-acquired pneumonia and ventilator-associated pneumonia  
 253 (HAP/VAP) (Bruss et al., 2021), making this drug eligible for fast-track evaluation. MRX8, another  
 254 polymyxin B derivative, started its clinical development on November 2020 (NCT04649541). MRX-  
 255 8 was developed using a “soft drug design” which represents a new approach to designing safer drugs  
 256 by integrating metabolism and detoxification factors into the drug design process (Lepak et al., 2020).

## 257 ANTIBIOTICS WITH A NEW MODE OF ACTION FOR MDR GRAM-NEGATIVE 258 BACTERIA

259 Among bacterial targets, peptidoglycan (PG) synthesis remains a privileged target with investigations  
 260 on molecules of the  $\beta$ -lactams family. One field of development focuses on the modification active  $\beta$ -  
 261 lactams by addition of an iron-chelating molecule, facilitating transport into bacteria (De Carvalho and  
 262 Fernandes, 2014). Cefiderocol, a first in class of siderophore-cephalosporins, is able to bind to

263 extracellular free iron, allowing active transport into the periplasmic space of Gram-negative bacteria  
 264 through siderophore uptake systems. Cefiderocol subsequently binds to penicillin binding proteins  
 265 (PBPs), inhibiting bacterial PG cell wall synthesis which leads to cell lysis and death (EMA, 2020).  
 266 Although siderophore-antibiotics have been investigated for several decades, none of them progressed  
 267 to clinical development because of poor correlation between *in vitro* activity and *in vivo* efficacy or  
 268 because of toxicity (El-Lababidi. and Rizk, 2020). Promising assessment of cefiderocol for the  
 269 treatment of cUTI in patients at risk of MDR Gram-negative infections started in phase II trial in 2015  
 270 (Portsmouth et al., 2018).

271 Lipopolysaccharide (LPS) that constitutes the OM outer layer at the surface of Gram-negative bacteria  
 272 represents also an attractive target against pathogens (MacNair et al., 2020). By binding to the LPS  
 273 transport protein D (LptD), the small cyclic peptide murepavadin causes a specific *P. aeruginosa* LPS  
 274 biogenesis alteration (Martin-Loeches et al., 2018). A second phase II study of murepavadin co-  
 275 administered with SOC in VAP due to *P. aeruginosa* finished in 2017 (NCT02096328).

### 276 **But what's new in the development pipeline since the 2017 WHO alert?**

277 In 2018, phase II results of cefiderocol versus imipenem-cilastatin, an available therapy for the  
 278 treatment of cUTI were published. Response rates for the composite endpoint of microbiological  
 279 eradication and clinical response were significantly higher in the cefiderocol arm compared with  
 280 imipenem-cilastatin arm establishing the non-inferiority of cefiderocol (Portsmouth et al., 2018). The  
 281 safety profile of cefiderocol in this study was good. On the basis of these results, cefiderocol was given  
 282 priority review and was the first siderophore-antibiotic approved by the FDA in 2019<sup>1</sup>, providing a  
 283 new option of treatment of cUTI including pyelonephritis in patient with limited or no alternative  
 284 treatment (FDA, 2019). Evaluated as non-inferior to meropenem for the primary endpoint of all-cause  
 285 mortality in a phase III trial, cefiderocol has obtained an expanded indication for HAP and VAP (FDA,  
 286 2020; Wunderink et al., 2021). However, an increase in all-cause mortality death and infection-related  
 287 death with treatment failure was observed in patients treated with cefiderocol compared with best  
 288 available therapy in a descriptive phase III trial in critically ill patients with Gram-negative CR  
 289 bacterial infections (Bassetti et al, 2021). The cause of the increase in mortality has not been established  
 290 but close monitoring of the clinical response to therapy in patients with cUTI and HAP/VAP was asking  
 291 by FDA (FDA, 2020). In 2020, the Committee for Medicinal Products for Human Use (CHMP)  
 292 adopted a positive opinion, recommending the granting of a marketing authorization in Europe. The  
 293 overall nonclinical and clinical data support the ability of cefiderocol to address an unmet need. The  
 294 balance of benefits and risks is considered positive (EMA, 2020).

295 Murepavadin fulfilled innovation criteria (WHO 2019), including the main criteria for absence of  
 296 known cross-resistance (Burrows, 2018), and reached phase III trials in HAP/VAP caused by *P.*  
 297 *aeruginosa* (NCT03582007, NCT03409679). Unfortunately, murepavadin was prematurely withdrawn  
 298 from the authorization race on July 2019 due to high incidence of kidney injury<sup>2</sup>, another hard reality  
 299 of clinical development that can be interrupted even in late phase due to imbalance of benefit/risk ratio  
 300 for patients. An alternative mode of administration of murepavadin, such as inhalation, is being  
 301 explored to improve nephrotoxicity. A new phase I has been announced to start in 2022<sup>3</sup>. In 2019,  
 302 RC01 another new antibiotic targeting LPS biogenesis entered in clinical development (**Figure 4B**).  
 303 RC01 inhibits the bacterial enzyme LpxC, a key protein involved in the production of LPS lipid A.  
 304 Despite demonstrated efficacy in clinical isolates of *P. aeruginosa* from CF patients and good safety  
 305 in preclinical phases, the phase I prematurely stopped for safety concerns (NCT03832517). As

306 <sup>1</sup>FDA News Release December 16, 2019. <https://www.fda.gov/news-events/press-announcements/fda-approves-new-antibacterial-drug-treat-complicated-urinary-tract-infections-part-ongoing-efforts> [Accessed December 2021]

307 <sup>2</sup>Polyphor website: <https://www.polyphor.com/news/corporate-news-details/?newsid=1800485> [Accessed December 2021]

308 <sup>3</sup>Polyphor website: <https://www.polyphor.com/news-adhoc/news-detail/?newsid=2176875> [Accessed December 2021]

## 309 NEW COMBINATIONS OF $\beta$ -LACTAM/ $\beta$ -LACTAMASE INHIBITOR: A STRATEGY TO 310 GET AROUND RESISTANCE

311 Among antibiotics,  $\beta$ -Lactam targets specifically the PG biosynthesis through covalent  
312 binding/interaction to PBPs, the enzyme involved in late stages of PG synthesis. However, bacteria  
313 under selection pressure could produce  $\beta$ -lactamases, enzymes who hydrolyzed the  $\beta$ -Lactam ring.  
314 Hydrolyzing  $\beta$ -lactam antibiotics has made many of them ineffective becoming a major resistance issue  
315 in Gram-negative bacteria (Tümmler, 2019). Consequently, a synergic combination of  $\beta$ -lactam and an  
316 appropriate  $\beta$ -lactamase inhibitor (BLI) restoring  $\beta$ -lactam activity is a frequently used strategy. The  
317 well-known combination amoxicillin ( $\beta$ -lactam)/clavulanic acid (BLI) is a good example as it  
318 represents one of the most prescribed antibiotic worldwide and is a WHO-designed “core access  
319 antibiotic” that should be consistently available (Sharland et al., 2018).

320 Relebactam is a new BLI with activity against a broad range of  $\beta$ -lactamase enzymes including  
321 carbapenemases (Smith et al. 2020). *In vitro* addition of relebactam to imipenem restored imipenem  
322 activity against several imipenem-resistant bacteria, including *P. aeruginosa* (Smith et al. 2020).  
323 Relebactam in association with imipenem-cilastatin demonstrated efficacy in phase II trials dedicated  
324 to complicated urinary tract infections (cUTIs) (Sims et al., 2017) and complicated intraabdominal  
325 infections (cIAIs) (Lucasti et al., 2016), thus entered in phase III trial in HAP/VAP (Titov et al., 2020)  
326 *versus* piperacillin-tazobactam and imipenem-resistant pathogens *versus* colistin (Motsch et al., 2020),  
327 a polymixin used as last resort therapy. Taniborbactam is a highly potent pan-spectrum new BLI that  
328 inhibits all classes of  $\beta$ -lactamase enzymes (Liu et al., 2020). In combination with the fourth-generation  
329 cephalosporin cefepime, taniborbactam positively completed the phase I milestone in 2017 and thus  
330 supported other trials (Dowell et al., 2020).

### 331 **But what’s new in the clinical development pipeline since the 2017 WHO alert**

332 Evaluation of phases II/III clinical data (Sims et al., 2017; Lucasti et al., 2016; Titov et al., 2020;  
333 Motsch et al., 2020) demonstrates that the relebactam/imipenem-cilastatin association is well tolerated  
334 and effective in the treatment of cUTIs, cIAIs, HAP/VAP and obtained FDA approval for these  
335 therapeutic indications<sup>1,2</sup>. Taniborbactam/cefepime association demonstrated *in vitro* rescue of  
336 cefepime activity by taniborbactam against clinical isolates of CRPA (Hamrick et al., 2020). Fast Track  
337 designated by the FDA, the association skipped phase II and is currently on phase III trial to access the  
338 safety and efficacy compared with meropenem in both eradication of bacteria and in symptomatic  
339 response as primary endpoint in patients with cUTIs including acute pyelonephritis (NCT03840148).  
340 Another phase III trial in patients with HAP/VAP is scheduled to begin in 2022<sup>3</sup>. At least four other  
341 new BLI in association with  $\beta$ -lactam are on phase I stage (completed or ongoing) (**Figure 4C**):  
342 nacubactam, zidebactam, QPX7728 and XNW4107. Whereas nacubactam reported narrow *in vitro*  
343 activity in *P. aeruginosa* (Asempa et al., 2020), QPX7728 is an ultra-broad-spectrum  $\beta$ -lactamase  
344 inhibitor with the broadest spectrum of inhibition *in vitro* reported to date in a single BLI molecule  
345 (Lomovskaya et al. 2020). Zidebactam in association with cefepime should start a phase III in cUTI or  
346 acute pyelonephritis end of 2021 (NCT04979806). Despite this antibiotic-based strategy, other  
347 mechanisms can unfortunately confer resistance to  $\beta$ -lactam/BLI new combinations. Beyond  $\beta$ -  
348 lactamases production, overproduction or extended-spectrum  $\beta$ -lactamases, *P. aeruginosa* has  
349 developed efficient mechanisms as decreased permeability of the outer membrane and overproduction  
350 of efflux pumps (Moradali et al., 2017).

<sup>1</sup>FDA website: [FDA approves new treatment for complicated urinary tract and complicated intra-abdominal infections](#) | FDA [accessed December 2021]

<sup>2</sup>FDA website: [FDA Approves Antibiotic to Treat Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia](#) | FDA [Accessed December 2021]

<sup>3</sup>Venatorx website: <https://www.venatorx.com/press-releases/venatorx-pharmaceuticals-provides-update-on-cefepime-taniborbactam/> [Accessed December 2021]

352 Bacteriophages that infect and lyse their target bacteria are being reconsidered as an alternative therapy  
 353 to treat MDR bacterial infections. Interestingly, some phages are also able to disrupt biofilm barrier  
 354 with EPS-depolymerase activity (Cornelissen et al., 2012). Phage therapy includes mono-phage,  
 355 phages-cocktail, phage-derived enzyme (lysin), bio-engineered phage and phage combined with  
 356 antibiotics (Patil et al., 2021). Systematic literature search shows a large number of case study reports  
 357 and compassionate use for severe patients in specialized centers but despite promising results recent  
 358 clinical trial evidence-based will be necessary. The first randomized controlled trial using a cocktail of  
 359 natural lytic *P. aeruginosa* phages for the topical treatment of infected burn wound patients, was  
 360 stopped on January 2017 because of PP1131 insufficient efficacy versus SOC (Jault et al., 2019).

### 361 **But what's new in the clinical development pipeline since the 2017 WHO alert?**

362 In 2019, full results of the phase I/II trial testing PP1131 were published. This study had several  
 363 limitations and encountered many unexpected difficulties. An ancillary analysis showed that the  
 364 bacteria isolated from patients with failed PP1131 treatment were resistant to low phage doses  
 365 (Jault et al., 2019). Phage cocktails of predefined composition could negatively interfere in the relations  
 366 between phage and bacterium by selecting phage resistance in the bacterial populations that vary  
 367 among patients (Tümmler, 2019). An individually approach could be a more effective using  
 368 phagograms to study *in vitro* the sensitivity of *P. aeruginosa* to bacteriophages in the manner of  
 369 antibiograms, and a phage collection for personalized treatment (Friman et al., 2016).

370 APPA02<sup>1</sup>, a new inhaled cocktail of complementary phages, is currently tested for safety and  
 371 tolerability in a phase I/II trial to treat serious respiratory infections, with an initial emphasis on CF  
 372 patients (NCT04596319). *P. aeruginosa* recovery in sputum following multiple doses of treatment will  
 373 be also explored. In March 2021, a phase I/II trial was initiated for assessment of another targeted  
 374 inhaled phage therapy YPT01<sup>2</sup> added to standard antimicrobial therapy in the treatment of chronic *P.*  
 375 *aeruginosa* infections in CF (NCT04684641). A multispecies targeting topic phage cocktail TP102<sup>3</sup>  
 376 was formulated against *P. aeruginosa* but also *Staphylococcus aureus* and *Acinetobacter baumannii*.  
 377 TP102 started a safety evaluation in subjects with both non-infected and infected diabetic foot ulcers  
 378 as the primary endpoint and targeted bacteria clearance as secondary endpoint (NCT04803708).  
 379 Results of these 3 early phase studies for APPA02, YPT01 and TP102 assessment are expected in 2022.  
 380 BX004-A, a nebulized bacteriophage therapy entered in a phase Ia/Iib (**Figure 4D**). Exploratory  
 381 objectives include whether this treatment reduces sputum *P. aeruginosa* bacterial load in CF subjects  
 382 with chronic *P. aeruginosa* pulmonary infection (NCT05010577). During the same time, other new  
 383 topical phage therapies by spray as an adjunct to SOC therapy for the prevention and treatment of *P.*  
 384 *aeruginosa*, *S. aureus*, or *Klebsiella pneumoniae* infections will enter in development in pressure ulcers  
 385 (PL03BM, NCT04815798) and burns (PGX0100, NCT04323475). Despite promising results, both  
 386 historically and recently, the efficacy of phage therapy has still not been sufficiently examined and  
 387 documented in high-quality clinical trial in humans to answer the questions raised about how to best  
 388 use bacteriophages (Leitner et al., 2021).

### 389 **DEPRIVING BACTERIA FROM A SURVIVAL ESSENTIAL ELEMENT: IRON**

390 As an essential nutrient for growth and biofilm establishment, *P. aeruginosa* has developed different

391 <sup>1</sup>Armata Pharmaceutical website : <https://www.armatapharma.com/pipeline/ap-pa02/> [Accessed December 2021]

392 <sup>2</sup>Felix Biotechnology website : <https://www.felixbt.com/new-page> [Accessed December 2021]

393 <sup>3</sup>Technophage website: <http://technophage.pt/pipeline/> [Accessed December 2021]

394 2021). Acting as an iron mimetic, gallium disrupts multiple iron-dependent synthetic and metabolic

nd  
ng  
il.,

395 pathways (Frei, 2020). Preliminary clinical study raised the possibility that gallium may be a safe and  
 396 effective treatment for human infections (Goss et al., 2018). A phase II study to test IV gallium nitrate  
 397 to control *P. aeruginosa* infections in adults with CF started in 2016 (NCT02354859). Because the IV  
 398 form of gallium involves a continuous 5-days infusion, which is a demanding treatment regimen for  
 399 patients, the AR501 inhaled formulation of gallium citrate self-administered via a nebulizer device was  
 400 designed to be given once a week, allowing for direct delivery to the lungs<sup>1</sup>. Another antimicrobial  
 401 with an activity on iron metabolism is ALX-009, a combination of lactoferrin and hypothiocyanite,  
 402 natural major antimicrobial substances deficient in the airway secretions of CF patients (Tunney et al.,  
 403 2018). Lactoferrin deprive bacteria of iron due to its iron chelator activity and can bind to cell  
 404 membranes leading to alterations in permeability and enhancing bacterial killing by other antibiotics  
 405 (Rogan et al., 2004). Hypothiocyanite is a highly reactive compound that oxidizes proteins to create  
 406 disulfide bonds that perturb the bacterial physiology (Thomas et al., 1978). ALX009 started a phase I  
 407 in 2015 as an inhalable solution administered through nebulization (NCT02598999).

#### 408 **But what's new in the clinical development pipeline since the 2017 WHO alert?**

409 The phase II clinical trial in adults with CF found no significant difference between the number of  
 410 responders (defined as a participant having a 5% or greater increase in lung function by day 28) in the  
 411 IV gallium nitrate and placebo group<sup>1</sup>. The primary endpoint was unmet, however a significantly  
 412 reduction of *P. aeruginosa* was found in the sputum of gallium treated patients compared to the placebo  
 413 group for participants who were culture positive for *P. aeruginosa* at baseline<sup>2</sup>. Overall, IV gallium  
 414 nitrate was well-tolerated compared to placebo. With broad-spectrum anti-infective activity AR501 is  
 415 being developed in a phase I/IIa (**Figure 4D**) to treat chronic bacterial lung infections of CF patients  
 416 (NCT03669614). On 2020 positive safety data were reported from the phase I portion of the study, and  
 417 AR-501 has been granted Fast Track, Qualified Infectious Disease Product, and Orphan Drug  
 418 Designation by FDA and EMA. The originally planned protocol design was adapted into a phase IIa  
 419 (dose selection / sample size determination) which results expected in 2022 will be implemented  
 420 directly in a phase IIb study (efficacy) using the same clinical study protocol<sup>3</sup>. This is an encouraging  
 421 example of simplified and accelerated development supported by Health Authorities in a context of  
 422 urgent need. Final data collection date for primary outcome measure of ALX009 in healthy volunteers  
 423 and patients suffering from CF and non-CF bronchiectasis was expected in October 2021  
 424 (NCT02598999).

#### 425 **ANTI-BIOFILM STRATEGY**

426 Among virulence factors of *P. aeruginosa*, biofilms increase bacterial adherence, immune system  
 427 evasion and antibiotic tolerance by blocking the diffusion of positively charged drugs. OligoG is an  
 428 alginate oligosaccharide with the potential to reduce sputum viscosity of CF patients by chelating  
 429 calcium (Ermund et al., 2017), easing clearance of mucus from patient airways, reducing microbial  
 430 burden and inflammation. OligoG was also shown to disrupt biofilm structure of *P. aeruginosa* mucoid  
 431 phenotype (Powell et al., 2018) and could in consequence improve host immune system action and the  
 432 effectiveness of antimicrobial agents. To determine the safety and local tolerability of multiple dose  
 433 administration of inhaled fragment in healthy volunteers, a phase I study was performed with a  
 434 particular attention on pulmonary functioning and adverse events (NCT00970346).

435 <sup>1</sup>Aridis pharmaceutical website : <https://www.aridispharma.com/ar-501/> [Accessed December 2021]

436 <sup>2</sup>Cystic Fibrosis Foundation website : <https://www.cff.org/Trials/Finder/details/374/IGNITE-Safety-and-effectiveness-of-gallium-nitrate-in-adults-with-cystic-fibrosis> [Accessed December 2021]

437 <sup>3</sup>Aridis Pharmaceuticals website: [Aridis Announces Agreement with the FDA on Updated Phase 2 Clinical Trial Design for AR-501 - Sep 8, 2020 \(aridispharma.com\)](https://www.aridispharma.com) [Accessed December 2021]

438 FEV<sub>1</sub> (forced expiratory volume by the patient in one second) was not reached <sup>[1,2]</sup>. Lung function is

439 widely used as primary outcome measure in the development of drugs to treat CF but regarding its  
440 mode of action could not be adapted to prove an OligoG efficacy, especially when disease is already  
441 installed. *Post hoc* subgroup analyses support mechanism of action for OligoG and warrant further  
442 prospective studies (Van Koningsbruggen-Rietschel et al., 2020). OligoG has Orphan Drug designation  
443 from both the EMA and the FDA and is currently tested in other phase IIb studies in addition to SOC  
444 compared to placebo with SOC too (NCT03698448 and NCT03822455). SNSP113 (SYGN113), a  
445 novel large polycationic glycopolymer, poly (acetyl, arginyl) glucosamine was tested in a phase  
446 I study in healthy subjects and patients with stable CF (NCT03309358) and is currently evaluated in a  
447 phase II study (**Figure 4E**). PLG0206 (WLB02), an engineered cationic antimicrobial peptide with  
448 broad-spectrum activity and preventing *in vitro* *P. aeruginosa* biofilm growth on airway epithelial cells  
449 (Lashua et al., 2016), received Orphan Drug status for prosthetic joint infection and entered in phase  
450 I trial in healthy subjects in 2018. PLG0206 will enter a phase Ib for treatment of periprosthetic joint  
451 infection in 2022 (NCT05137314).

## 452 OTHER INNOVATIVE ANTI-VIRULENCE STRATEGIES

453 As T3SS and associated toxins are major virulence factors of *P. aeruginosa* (**Figure 2**), innovative  
454 therapeutic strategies are developed to reduce the infection severity. Despite many hopes based on *in*  
455 *vitro* or preclinical activities, only one treatment targeting T3SS is currently in clinical development  
456 (**Figure 4E**). Ftortiazinon, a small molecule with a strong potential as an antibacterial therapy  
457 (Sheremet et al., 2020), developed by the Gamaleya Research Institute, entered a phase 2 in  
458 combination with cefepime for the treatment of patients with cUTI caused by *P. aeruginosa* in 2018  
459 (NCT03638830).

## 460 DISCUSSION

461 This review aimed at providing an up-to-date picture of therapeutics against *P. aeruginosa* currently  
462 in clinical development, since the 2017 WHO alert. Only one antibacterial drug with a new mode of  
463 action has been approved by FDA and EMA against *P. aeruginosa* (**Figure 4B**). Among 18 drugs of  
464 interest anti-*P. aeruginosa* in the development pipeline described in this review, only one new  
465 combination of  $\beta$ -lactam/ $\beta$ -lactamase inhibitor of antibiotics is in phase III trial (**Figure 4C**).  
466 Derivatives of existing antibiotics considered as “traditional agents” are highly represented (**Figure 5**).  
467 Diverse “non-traditional agents” including bacteriophages, iron mimetic/chelator and anti-virulence  
468 factors are significantly represented but unfortunately still in early clinical stages. There is no vaccine  
469 in development to prevent *P. aeruginosa* infections despite a half century of research effort specifically  
470 focused on this challenge (Sainz-Mejías et al., 2020; ClinicalTrials.gov., 2021).

471 Studying pipeline anti-*P. aeruginosa* since 2017 up to now, shows how development of a new  
472 treatment can be a difficult process. Lack of correspondence between *in vitro* or preclinical study and  
473 phase II clinical response questions the choice of pertinent animal models recreating human infection  
474 conditions (Theuretzbacher et al., 2019; Theuretzbacher et al., 2020). Methodology used is often a  
475 strategic issue, with the crucial definition of the clinically significant primary outcome (Adlbrecht et  
476 al., 2020; Merakou et al., 2018) and the infection-site that could best allow to meet efficacy criteria.  
477 The absence of statistically significant evidence is not the evidence of absence of efficacy. We can  
478 question for example if death is a good primary outcome when critically ill patients are entering in ICU  
479 (Merakou et al., 2018) and if lung function measure is a pertinent primary outcome for a CF patient  
480 with chronic severe disease (Ali et al., 2019; Van Koningsbruggen-Rietschel et al., 2020). Studying  
481 pipeline also underlines that a late clinical stage development can be interrupted due to unexpected

482 toxicity<sup>1</sup> or bankrupt of a biotechnology company. COVID-19 pandemic had also an important impact  
483 on clinical trials recruitment and timelines during the last 2 years.

484 *P. aeruginosa*–host interactions and host immunometabolism are not yet enough understood,  
485 complicating the development of effective therapies and vaccines (Sainz-Mejías et al., 2020). Due to  
486 the fact that *P. aeruginosa* is an opportunistic bacterium, patients infected with *P. aeruginosa* are  
487 mostly immunocompromised individuals. This make it difficult to develop a vaccine for these patients  
488 (Yaeger et al., 2021). As *P. aeruginosa* is characterized by its genomic plasticity, drugs or vaccine  
489 must be designed to target conserved elements between strains to ensure an optimal efficacy (Tse et  
490 al., 2017). This constitutes a true limitation regarding strains like PA7, a non-respiratory MDR that  
491 lacks the T3SS and its effectors or the exotoxin A (Roy et al., 2010) or the Liverpool epidemic strain,  
492 a lineage with enhanced virulence and antimicrobial resistance characteristics (Salunkhe et al., 2005).

493 Each class of treatment against *P. aeruginosa* presents strengths, weaknesses, opportunities and  
494 threatens that have to be taken into account in global clinical development considerations (**Figure 6**).  
495 Among “non-traditional agents”, a vaccine could offer a long-term sustainable approach to infection  
496 prevention because it will decrease the need for antibiotics and hence the emergence of  
497 antibioresistance (Micoli et al., 2021). Anti-virulence strategy may have the potential through novel,  
498 specialized and non-killing modes of action to reduce the selective pressure responsible of MDR  
499 (Dickey et al., 2017) or select less virulent strains. Regarding combinatory multifactorial virulence, an  
500 anti-virulence factor used alone do not has therapeutic utility and hence must be used as pre-emptive  
501 or adjunctive treatment in combination with traditional antibiotics (Dickey et al., 2017). Despite many  
502 years of research, no anti-virulent agent has yet been introduced in clinical use against *P. aeruginosa*.  
503 Novel targets for anti-virulence strategy must be proposed and T6SS as a key virulence factor of *P.*  
504 *aeruginosa* (**Figure 2**) could be selected. Inhibition of T6SS assembly or neutralization of its toxins  
505 (amidases, phospholipases, protease, pore forming toxin and iron-acquisition effector) (**Figure 2**)  
506 would allow to interfere at two moments of the infectious process: (i) during host colonization  
507 (competition for the niche with microbiota or other pathogens in case of CF patients) and (ii) escape  
508 from the immune system (internalization and autophagy).

509 Current antibiotics are less effective due to increasing resistance and some *P. aeruginosa* isolates  
510 are resistant to all available treatments, underlying the unmet medical need. Given the development  
511 duration, the pipeline remains unsatisfactory leading best case to the approval of new antibacterial  
512 drugs that treat CRPA in several years. And as the United Nations, WHO and numerous experts  
513 published in an April 29, 2019, report, immediate, coordinated and ambitious action must be taken to  
514 avoid a potentially disastrous antimicrobial resistance crisis. If not, drug-resistant diseases could cause  
515 10 million deaths each year by 2050 warns the UN Inter-Agency Coordination Task Force on  
516 Antimicrobial Resistance<sup>1</sup>. Developing a new treatment takes years, however COVID-19 pandemic  
517 has demonstrated that it is possible to accelerate the development of a molecule or a vaccine in case of  
518 crisis (Krammer, 2020). Beyond the investments needed to build a robust pipeline, the Community  
519 need to reinvent medicine with new strategies of development to avoid the disaster.

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<sup>1</sup>WHO website news release on 29 April 2019: [New report calls for urgent action to avert antimicrobial resistance crisis \(who.int\)](https://www.who.int/news/item/29-04-2019-new-report-calls-for-urgent-action-to-avert-antimicrobial-resistance-crisis) [Accessed December 2021]

526 **FIGURE LEGENDS**

527 **FIGURE 1. Clinical manifestations of *P. aeruginosa* infections.** Representation of human body site  
 528 infections and main clinical manifestations of *P. aeruginosa*. Healthcare-associated infections  
 529 highlighted in blue illustrate the significant burden of *P. aeruginosa* on invasive acts, surgery, devices  
 530 use resulting in local or systemic complications (Dando et al., 2014 ; Shrestha et al., 2021; Durand,  
 531 2017; Arsovic et al., 2020; Ramireddy et al., 2020; Elborn, 2016; Chai and Xu, 2020; Shukla et al.,  
 532 2020; Jean et al., 2020; Montravers et al., 2020; Wu et al., 2011; Gahlot et al., 2014, Newman et al.,  
 533 2017; Cerioli et al., 2020; Vieira et al., 2016; Hauser and Ozer, 2011).

534 **FIGURE 2. Key virulence factors of *P. aeruginosa*.** Schematic representation of cell associated and  
 535 extracellular relevant virulence factors and their main roles on *P. aeruginosa* pathogenesis. OMPs,  
 536 outer membrane proteins; LPS, lipopolysaccharide; ROS, reactive oxygen species; EPS,  
 537 exopolysaccharides; eDNA, extracellular desoxyribonucleic acid; T4P, type 4 pili; TnSS, type n  
 538 secretion system; ETA, exotoxin A; PVD, pyoverdine; PCH, pyochelin; PCN; pyocyanin; PG,  
 539 peptidoglycan; ECM, extracellular (Alhazmi, 2015; Jurado-Martín et al., 2021; Sana et al., 2016; Berni  
 540 et al., 2019; Nolan et al., 2021).

541 **FIGURE 3. Review focus, data search criteria and strategy.**

542  
 543 **FIGURE 4A. Search results: anti-*Pseudomonas aeruginosa* clinical development pipeline in**  
 544 **December 2021.** MoA, mode of action; IM, intramuscular; IV, intravenous; Ig; immunoglobulin;  
 545 mAb, monoclonal antibody; pAb, polyclonal antibody; eDNA, extracellular desoxyribonucleic acid.

546 **FIGURE 4B. Search results: anti-*Pseudomonas aeruginosa* clinical development pipeline in**  
 547 **December 2021.** MoA, mode of action; IV, intravenous; PG, peptidoglycan; LPS,  
 548 lipopolysaccharide.

549 **FIGURE 4C. Search results: anti-*Pseudomonas aeruginosa* clinical development pipeline in**  
 550 **December 2021.** MoA, mode of action; IV, intravenous; PG, peptidoglycan.

551 **FIGURE 4D. Search results: anti-*Pseudomonas aeruginosa* clinical development pipeline in**  
 552 **December 2021.** MoA, mode of action; IV, intravenous.

553 **FIGURE 4E. Search results: anti-*Pseudomonas aeruginosa* clinical development pipeline in**  
 554 **December 2021.** MoA, mode of action; IV, intravenous; T3SS, type 3 secretion system.

555 **FIGURE 5. Anti-*Pseudomonas aeruginosa* treatments in clinical development in December**  
 556 **2021.**

557 **TABLE 1. Strengths and weaknesses (internal factors), opportunities and threats (external**  
 558 **factors) of each class of treatment in clinical development against *P. aeruginosa*.** This table is  
 559 based on the following references for vaccines (Theuretzbacher et al., 2020; Micoli et al., 2021; Sainz-  
 560 Mejías et al., 2020 ; Merakou et al., 2018 ; Bianconi et al., 2019 ; Antonelli et al., 2021), antibodies  
 561 (Theuretzbacher et al., 2020 ; Yaeger et al., 2021; Adlbrecht et al., 2020 ; Lakemeyer et al., 2018;  
 562 Zurawski et al., 2020), polymyxins (Li, et al., 2019; Theuretzbacher et al., 2020; Lepak et al., 2020),  
 563 new antibiotics (WHO, 2021; Dickey et al, 2017; Tse et al., 2017), new combinations of  $\beta$ -lactam/ $\beta$ -  
 564 lactamase inhibitor (WHO, 2021 ; Theuretzbacher et al., 2020), phages (Patil et al., 2021; Jault et al.,  
 565 2019; Friman et al., 2016), iron metabolism disruption (Zhang et al., 2021; Frei et al., 2020), anti-

566 biofilm (Dickey et al., 2017), other anti-virulence factors (Dickey et al., 2017, Theuretzbacher et al.,  
567 2020).

Type	Strengths	Weaknesses	Opportunities	Threats
<b>Vaccines</b>	<ul style="list-style-type: none"> <li>- Prophylactic strategy with a response in early stage of infection</li> <li>- Multitargeting possible/specificity</li> <li>- Reduced probability of resistance</li> <li>- Well define target population (high risks patients for opportunistic infection to improve immunity)</li> </ul>	<ul style="list-style-type: none"> <li>- Non immediate action</li> <li>- Limited predictive value of animal models (immune system complexity)</li> <li>- Weak preclinical pipeline</li> <li>- No vaccine currently in clinical trial</li> <li>- Immunisation dependent of the patient immune system status</li> </ul>	<ul style="list-style-type: none"> <li>- COVID-19 vaccine development change of paradigm</li> <li>- New technologies (reverse vaccinology, adjuvants optimization, mRNA)</li> <li>- Spread of MDR as a reason to consider vaccination</li> </ul>	<ul style="list-style-type: none"> <li>- Image of low morbidity/mortality of <i>P. aeruginosa</i> infection in general population</li> <li>- Burden of disease and incidence rate not well define in high-risk patients</li> <li>- Development mostly in health-care associated pneumonia</li> <li>- Difficulties to generate robust data to support approval (how to design clinical trial regarding complexity of infections)</li> <li>- Non inferiority clinical trial (design strategy with lack of distinct benefit over existing treatment)</li> <li>- Non MDR arm used in the studies design; difficulties to recruit patients with MDR</li> <li>- Duration of clinical trial in the current development paradigm</li> <li>- High-risk strategies for innovative treatment (new targets or new type of drug; high attrition rate of phase I)</li> <li>- Cost of diagnosis before use of drugs with narrow spectrum</li> <li>- Cost of biotherapies manufacturing <i>versus</i> traditional drugs</li> <li>- Strong dependence on public and/or philanthropic funding</li> <li>- High need of innovation not or partially covered</li> <li>- Lack of commercial interest in developing new antibacterial drugs (high risk development, low return on investment expected, new drugs will be used as last resort)</li> <li>- Low economical value of novel antibiotic <i>versus</i> innovative treatment of chonical diseases</li> <li>- Many big pharmaceuticals companies abandoned R&amp;D programs</li> <li>- Challenge of clinical development by biotechnologies companies</li> </ul>
<b>Antibodies</b>	<ul style="list-style-type: none"> <li>- Immediate protection (preventive or adjunctive therapy possible)</li> <li>- Immunisation independent of the patient immune system status</li> <li>- Multitargeting possible/specificity</li> <li>- Anti-virulence factors strategy with probability of reduced resistance</li> <li>- Narrow spectrum avoiding the disruption of microbiota</li> </ul>	<ul style="list-style-type: none"> <li>- Mostly intravenous administration not ideal for immunocompromised patients</li> <li>- Large proteins</li> <li>- Usually narrow spectrum of activity necessitating diagnosis before to treat (specialized and costly health-care facilities)</li> </ul>	<ul style="list-style-type: none"> <li>- mAb technology well know in cancer or autoimmune diseases treatment</li> <li>- Manufacturing methods and safety profile well established</li> <li>- DNAmAb to overcome cost</li> </ul>	
<b>Polymyxins</b>	<ul style="list-style-type: none"> <li>- Broad-spectrum activity</li> <li>- Potentiate and extend the spectrum of conventional antibiotics (synergy)</li> <li>- Efficacy against both quiescent and growing bacteria</li> </ul>	<ul style="list-style-type: none"> <li>- Emergence of resistance</li> <li>- Large spectrum of activity engendering dysbiose</li> <li>- Possible toxicity against host</li> <li>- Currently last line of defense</li> </ul>	<ul style="list-style-type: none"> <li>- No newer alternatives : the urgent need to optimize their clinical use</li> <li>- Substantial progress made in understanding complexity of polymyxins and “soft drug design”</li> </ul>	
<b>New antibiotics (new MoA)</b>	<ul style="list-style-type: none"> <li>- New mode of action less susceptible to induce resistance</li> <li>- Broad or narrow activity spectrum</li> </ul>	<ul style="list-style-type: none"> <li>- Based on low evidence, clinicians appear reluctant to use new antibiotic agents</li> <li>- Safety profile less known</li> </ul>	<ul style="list-style-type: none"> <li>- Substantial knowledges of rich ecological niches that produces antibiotics as secondary metabolite</li> <li>- Human microbiota research enthusiasm</li> </ul>	
<b>New combinations of <math>\beta</math>-lactam/ <math>\beta</math>-lactamase inhibitor</b>	<ul style="list-style-type: none"> <li>- Synergic effect, restoring activity of <math>\beta</math>-lactam</li> <li>- Counteract <math>\beta</math>-lactamase defense strategy</li> </ul>	<ul style="list-style-type: none"> <li>- Resistance mechanisms beyond the production of <math>\beta</math>-lactamases</li> <li>- Broad-spectrum of antibiotic resistance/cross resistance</li> <li>- Short term option</li> </ul>	<ul style="list-style-type: none"> <li>- Highly developed antibacterial <math>\beta</math>-lactam based clinical pipeline.</li> </ul>	
<b>Phages</b>	<ul style="list-style-type: none"> <li>- Self amplification at infection site</li> <li>- Biofilm penetration (possible lysis)</li> <li>- Specificity of action avoiding microbiome disruption</li> <li>- Escape mutants could be less pathogenic due to loss of surface factors expression</li> </ul>	<ul style="list-style-type: none"> <li>- Lack of knowledge about phage mode of action</li> <li>- Strong selective pressure to develop resistance</li> <li>- Diagnosis necessary for personalized therapy</li> <li>- Immunogenicity of phage</li> </ul>	<ul style="list-style-type: none"> <li>- Availability for patients in Eastern Europe specialized centers</li> <li>- Companionate use as clinical experience</li> <li>- Cost effective</li> <li>- Human microbiome research (including largely phagome)</li> </ul>	
<b>Iron metabolism disruption</b>	<ul style="list-style-type: none"> <li>- Activity against Gram-negative and Gram-positive (broad spectrum of activity)</li> </ul>	<ul style="list-style-type: none"> <li>- Production of high level of siderophore pyoverdine to compensate</li> <li>- Lack of knowledges about exact mode of action</li> </ul>	<ul style="list-style-type: none"> <li>- Untapped potential of metal-based antibiotics versus organics compounds</li> </ul>	
<b>Anti-biofilm</b>	<ul style="list-style-type: none"> <li>- Sensibilize bacteria to antibiotic</li> <li>- Strategy with reduced probability of resistance</li> <li>- Can supplement antibiotics for increase efficacy</li> <li>- Specificity of action avoiding microbiota depletion</li> </ul>	<ul style="list-style-type: none"> <li>- Requires a combination therapy</li> <li>- Effective in strain infection with mucoid phenotype</li> </ul>	<ul style="list-style-type: none"> <li>- Substantial knowledges of virulence mechanisms of pathogen bacteria</li> <li>- Biofilm well recognized as a threat in healthcare institutions</li> </ul>	
<b>Other anti-virulence factors</b>	<ul style="list-style-type: none"> <li>- Strategy with reduced probability of resistance or selection of less virulent strains</li> <li>- Specificity of action avoiding microbiota depletion</li> </ul>	<ul style="list-style-type: none"> <li>- Diagnosis necessary for personalized therapy</li> <li>- Plasticity of virulence factors expression</li> <li>- Require a combination therapy</li> </ul>	<ul style="list-style-type: none"> <li>- The rise of antivirulence strategy (large number of putative virulence targets)</li> <li>- Antivirulence drugs already approved (exotoxins blockage)</li> </ul>	

568

569 **CONFLICT OF INTEREST**

570 The authors declare that the research was conducted in the absence of any commercial or financial  
571 relationships that could be construed as a potential conflict of interest. S.R. is currently working in the  
572 Medical Department of Novartis Gene Therapies France SAS as Senior Medical Science Manager. S.  
573 R. is a PhD student independently of his professional position and on a totally different therapeutic  
574 area.

575 **AUTHORS CONTRIBUTIONS**

576 S. R., A. L. G. and S. B. wrote the manuscript.

577 **REFERENCES**

- 578 Adlbrecht, C., Wurm, R., Depuydt, P., Spapen, H., Lorente, J. A., Staudinger, T. et al. (2020). Efficacy,  
579 immunogenicity, and safety of IC43 recombinant *Pseudomonas aeruginosa* vaccine in mechanically  
580 ventilated intensive care patients-a randomized clinical trial. *Crit. Care.* 24(1):74. doi: 10.1186/s13054-  
581 020-2792-z.
- 582 Alhazmi, A. (2015). *Pseudomonas aeruginosa* – Pathogenesis and Pathogenic Mechanisms.  
583 *International Journal of Biology*; 7, 44-67. doi:10.5539/ijb.v7n2p44.
- 584 Ali, S. O., Yu, X. Q., Robbie, G. J., Wu, Y., Shoemaker, K., Yu, L, et al. (2019). Phase 1 study of  
585 MEDI3902, an investigational anti-*Pseudomonas aeruginosa* PcrV and Psl bispecific human  
586 monoclonal antibody, in healthy adults. *Clin. Microbiol. Infect.* 2019 May;25(5):629.e1-629.e6. doi:  
587 10.1016/j.cmi.2018.08.004.
- 588 Antonelli, G., Cappelli, L., Cinelli, P., Cuffaro, R., Manca, B., Nicchi, S. et al. (2021). Strategies to  
589 Tackle Antimicrobial Resistance: The Example of *Escherichia coli* and *Pseudomonas aeruginosa*. *Int.*  
590 *J. Mol. Sci.* 22(9):4943. doi: 10.3390/ijms22094943.
- 591 Arsovic, N., Radivojevic, N., Jesic, S., Babac, S., Cvorovic, L., Dudvarski, Z. (2020). Malignant Otitis  
592 Externa: Causes for Various Treatment Responses. *J. Int. Adv. Otol.* 16(1):98-103. doi:  
593 10.5152/iao.2020.7709.
- 594 Asempa, T. E., Motos, A., Abdelraouf, K., Bissantz, C., Zampaloni, C., Nicolau, D. P. (2020).  
595 Meropenem-nacubactam activity against AmpC-overproducing and KPC-expressing *Pseudomonas*  
596 *aeruginosa* in a neutropenic murine lung infection model. *Int. J. Antimicrob. Agents* 55(2):105838.  
597 doi: 10.1016/j.ijantimicag.2019.10.019.
- 598 Bassetti, M., Echols, R., Matsunaga, Y., Ariyasu, M., Doi, Y., Ferrer, R., et al. (2021). Efficacy and  
599 safety of cefiderocol or best available therapy for the treatment of serious infections caused by  
600 carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label,  
601 multicentre, pathogen-focused, descriptive, phase 3 trial. *Lancet Infect. Dis.* 21(2):226-240. doi:  
602 10.1016/S1473-3099(20)30796-9.
- 603 Berni, B., Soscia, C., Djermoun, S., Ize, B., Bleves, S. (2019). A Type VI Secretion System Trans-  
604 Kingdom Effector Is Required for the Delivery of a Novel Antibacterial Toxin in *Pseudomonas*  
605 *aeruginosa*. *Front. Microbiol.* 10:1218. doi: 10.3389/fmicb.2019.01218.

- 606 Bianconi, I., Alcalá-Franco, B., Scarselli, M., Dalsass, M., Buccato, S., Colaprico, A., Marchi, S.,  
607 Massignani, V., Bragonzi, A. (2019). Genome-Based Approach Delivers Vaccine Candidates  
608 Against *Pseudomonas aeruginosa*. *Front. Immunol.* 9:3021. doi: 10.3389/fimmu.2018.03021.
- 609 Brown, P., Abbott, E., Abdulle, O., Boakes, S., Coleman, S., Divall, N. et al. (2019). Design of Next  
610 Generation Polymyxins with Lower Toxicity: The Discovery of SPR206. *ACS Infect. Dis.* 5(10):1645-  
611 1656. doi: 10.1021/acsinfecdis.9b00217.
- 612 Bruss, J., Lister, T., Gupta, V. K., Stone, E., Morelli, L., Lei, Y. et al. (2021). Single- and Multiple-  
613 Ascending-Dose Study of the Safety, Tolerability, and Pharmacokinetics of the Polymyxin Derivative  
614 SPR206. *Antimicrob. Agents Chemother.* 65(10):e0073921. doi: 10.1128/AAC.00739-21.
- 615 Burrows, L. L. (2018). The Therapeutic Pipeline for *Pseudomonas aeruginosa* Infections. *ACS Infect.*  
616 *Dis.* 4(7):1041-1047. doi: 10.1021/acsinfecdis.8b00112.
- 617 Cerioli, M., Batailler, C., Conrad, A., Roux, S., Perpoint, T., Becker, A., et al. (2020). *Pseudomonas*  
618 *aeruginosa* Implant-Associated Bone and Joint Infections: Experience in a Regional Reference Center  
619 in France. *Front. Med. (Lausanne)* 7:513242. doi: 10.3389/fmed.2020.513242.
- 620 Chai, Y. H. and Xu, J. F. (2020). How does *Pseudomonas aeruginosa* affect the progression of  
621 bronchiectasis? *Clin. Microbiol. Infect.* 26(3):313-318. doi: 10.1016/j.cmi.2019.07.010.
- 622 Chastre, J., François, B., Bourgeois, M., Komnos, A., Ferrer, R., Rahav, G. et al. (2020). Efficacy,  
623 Pharmacokinetics (PK), and Safety Profile of MEDI3902, an Anti-*Pseudomonas*  
624 *aeruginosa* Bispecific Human Monoclonal Antibody in Mechanically Ventilated Intensive Care Unit  
625 Patients; Results of the Phase 2 EVADE Study Conducted by the Public-Private COMBACTE-  
626 MAGNET Consortium in the Innovative Medicines Initiative (IMI) Program, *Open Forum Infectious*  
627 *Diseases* 7(Issue Supplement 1): 377–S378. doi: [10.1093/ofid/ofaa439.829](https://doi.org/10.1093/ofid/ofaa439.829)
- 628 Corbett, D., Wise, A., Langley, T., Skinne, K., Trimby, E., Birchall, S., Doral, A. et al. (2017).  
629 Potentiation of Antibiotic Activity by a Novel Cationic Peptide: Potency and Spectrum of Activity of  
630 SPR741. *Antimicrob. Agents Chemother.* 61(8):e00200-17. doi: 10.1128/AAC.00200-17.
- 631 Cornelissen, A., Ceysens, P. J., Krylov, V. N., Noben, J. P., Volckaert, G., Lavigne, R. (2012).  
632 Identification of EPS-degrading activity within the tail spikes of the novel *Pseudomonas putida* phage  
633 AF. *Virology* 434(2):251-6. doi: 10.1016/j.virol.2012.09.030.
- 634 Dando, S. J., Mackay-Sim, A., Norton, R., Currie, B. J., St John, J. A., Ekberg, J. A et al. (2014).  
635 Pathogens penetrating the central nervous system: infection, pathways and the cellular and molecular  
636 mechanisms of invasion. *Clin. Microbiol. Rev.* 27(4):691-726. doi: 10.1128/CMR.00118-13.
- 637 De Carvalho, C. C. and Fernandes, P. (2014). Siderophores as "Trojan Horses": tackling multidrug  
638 resistance? *Front. Microbiol.* 5:290. doi: 10.3389/fmicb.2014.00290.
- 639 Dickey, S. W. and Cheung, G. Y. C. (2017). Otto M. Different drugs for bad bugs: antivirulence  
640 strategies in the age of antibiotic resistance. *Nat. Rev. Drug Discov.* 16(7):457-471. doi:  
641 10.1038/nrd.2017.23.
- 642 Dowell, J. A., Dickerson, D., Henkel, T. (2020). Safety and Pharmacokinetics in Human Volunteers of  
643 Taniborbactam (VNRX-5133), a Novel Intravenous  $\beta$ -Lactamase Inhibitor. *Antimicrob Agents*  
644 *Chemother.* 65(11):e0105321. doi: 10.1128/AAC.01053-21.
- 645 Durand, M. L. (2017). Bacterial and Fungal Endophthalmitis. *Clin. Microbiol. Rev.* 30(3):597-613.  
646 doi: 10.1128/CMR.00113-16.

- 647 Eckburg, P. B., Lister, T., Walpole, S., Keutzer, T., Utley, L., Tomayko, J. et al. (2019). Safety,  
648 Tolerability, Pharmacokinetics, and Drug Interaction Potential of SPR741, an Intravenous Potentiator,  
649 after Single and Multiple Ascending Doses and When Combined with  $\beta$ -Lactam Antibiotics in Healthy  
650 Subjects. *Antimicrob. Agents Chemother.* 63(9):e00892-19. doi: 10.1128/AAC.00892-19.
- 651 Elborn, J. S. (2016). Cystic fibrosis. *Lancet* 388(10059):2519-2531. doi: 10.1016/S0140-  
652 6736(16)00576-6.
- 653 El-Lababidi, R. M. and Rizk, J. G. (2020). Cefiderocol: A Siderophore Cephalosporin. *Ann.*  
654 *Pharmacother.* 54(12):1215-1231. doi: 10.1177/1060028020929988.
- 655 EMA, European Medicines Agency (2020). Fetroja product information last updated 28/07/2020.  
656 [http://www.ema.europa.eu/en/documents/product-information/fetroja-epar-product-](http://www.ema.europa.eu/en/documents/product-information/fetroja-epar-product-information_en.pdf)  
657 [information\\_en.pdf](http://www.ema.europa.eu/en/documents/product-information/fetroja-epar-product-information_en.pdf)
- 658 EMA, European Medicines Agency (2020). 27 February 2020 EMA/CHMP/73102/2020 Committee  
659 for Medicinal Products for Human Use. [https://www.ema.europa.eu/en/documents/smop-initial/chmp-](https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-fetroja_en.pdf)  
660 [summary-positive-opinion-fetroja\\_en.pdf](https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-fetroja_en.pdf)
- 661 Ermund, A., Recktenwald, C. V., Skjåk-Braek, G., Meiss, L. N., Onsøyen, E., Rye, P. D. et al. (2017).  
662 OligoG CF-5/20 normalizes cystic fibrosis mucus by chelating calcium. *Clin. Exp. Pharmacol. Physiol.*  
663 2017 Jun;44(6):639-647. doi: 10.1111/1440-1681.12744.
- 664 EU Clinical Trial register (2018). Final study report. [https://www.clinicaltrialsregister.eu/ctr-](https://www.clinicaltrialsregister.eu/ctr-search/rest/download/result/attachment/2011-000801-39/1/24990)  
665 [search/rest/download/result/attachment/2011-000801-39/1/24990](https://www.clinicaltrialsregister.eu/ctr-search/rest/download/result/attachment/2011-000801-39/1/24990)
- 666 FDA, US Food And Drug Administration (2019). Briefing Information for the October 16,  
667 2019 Meeting of the Antimicrobial Drugs Advisory Committee.  
668 <https://www.fda.gov/media/131703/download>
- 669 FDA, US Food And Drug Administration (2020). Highlights of prescribing information updated  
670 09/2020. [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/209445s002lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209445s002lbl.pdf)
- 671 Frei, A. (2020). Metal Complexes, an Untapped Source of Antibiotic Potential? *Antibiotics* (Basel)  
672 9(2):90. doi: 10.3390/antibiotics9020090.
- 673 French, S., Farha, M., Ellis, M. J., Sameer, Z., Côté, J. P., Cotroneo, N. et al. (2020). Potentiation of  
674 Antibiotics against Gram-Negative Bacteria by Polymyxin B Analogue SPR741 from Unique  
675 Perturbation of the Outer Membrane. *ACS Infect. Dis.* 2020 6(6):1405-1412. doi:  
676 10.1021/acsinfecdis.9b00159.
- 677 Friman, V. P., Soanes-Brown, D., Sierocinski, P., Molin, S., Johansen, H. K., Merabishvili, M. et al.  
678 (2016). Pre-adapting parasitic phages to a pathogen leads to increased pathogen clearance and lowered  
679 resistance evolution with *Pseudomonas aeruginosa* cystic fibrosis bacterial isolates. *J. Evol. Biol.*  
680 29(1):188-98. doi: 10.1111/jeb.12774.
- 681 Gahlot, R., Nigam, C., Kumar, V., Yadav, G., Anupurba, S. (2014). Catheter-related bloodstream  
682 infections. *Int. J. Crit. Illn. Inj. Sci.* 4(2):162-7. doi: 10.4103/2229-5151.134184.
- 683 Gessard, C. (1882). De la pyocyanine et de son microbe ; colorations qui en dépendent dans les  
684 liquides organiques. Applications cliniques. Medical Thesis.

- 685 Goss, C. H., Kaneko, Y., Khuu, L., Anderson, G. D., Ravishankar, S., Aitken, M. L. et al. (2018).  
 686 Gallium disrupts bacterial iron metabolism and has therapeutic effects in mice and humans with lung  
 687 infections. *Sci. Transl. Med.* 10(460):eaat7520. doi: 10.3390/antibiotics9020090.
- 688 Hamrick, J. C., Docquier, J. D., Uehara, T., Myers, C. L., Six, D. A., Chatwin, C. L. et al. (2020).  
 689 VNRX-5133 (taniborbactam), a broadspectrum inhibitor of serine- and metallo- $\beta$ -lactamases, restores  
 690 activity of cefepime in Enterobacterales and *Pseudomonas aeruginosa*. *Antimicrob. Agents*  
 691 *Chemother.* 64(3):e01963-19. doi: 10.1128/AAC.01963-19.
- 692 Hauser, R. A. and Ozer, A. E. (2011). *Pseudomonas aeruginosa*. *Nature Review Microbiology* 9 (3).
- 693 Jault, P., Leclerc, T., Jennes, S., Pirnay, J. P., Que, Y. A., Resch, G. et al. (2019). Efficacy and  
 694 tolerability of a cocktail of bacteriophages to treat burn wounds infected by *Pseudomonas aeruginosa*  
 695 (PhagoBurn): a randomised, controlled, double-blind phase 1/2 trial. *Lancet Infect. Dis.* 19(1):35-45.  
 696 doi: 10.1016/S1473-3099(18)30482-1.
- 697 Jean, S. S., Chang, Y. C., Lin, W. C., Lee, W. S., Hsueh, P. R., Hsu, C. W. (2020). Epidemiology,  
 698 Treatment, and Prevention of Nosocomial Bacterial Pneumonia. *J. Clin. Med.* 9(1):275. doi:  
 699 10.3390/jcm9010275.
- 700 Johansen, H. K. and Gøtzsche, P. C. (2015). Vaccines for preventing infection with *Pseudomonas*  
 701 *aeruginosa* in cystic fibrosis. *Cochrane Database Syst. Rev.* 2015(8):CD001399. doi:  
 702 10.1002/14651858.
- 703 Jurado-Martín, I., Sainz-Mejías, M., McClean, S. (2021). *Pseudomonas aeruginosa*: An Audacious  
 704 Pathogen with an Adaptable Arsenal of Virulence Factors. *Int. J. Mol. Sci.* 22(6):3128. doi:  
 705 10.3390/ijms22063128.
- 706 Krammer, F. (2020). SARS-CoV-2 vaccines in development. *Nature* 586(7830):516-527. doi:  
 707 10.1038/s41586-020-2798-3
- 708 Lakemeyer, M., Zhao, W., Mandl, F. A., Hammann, P., Sieber, S. A. (2018). Thinking Outside the  
 709 Box-Novel Antibacterials To Tackle the Resistance Crisis. *Angew Chem. Int. Ed. Engl.* 57(44):14440-  
 710 14475. doi: 10.1002/anie.201804971.
- 711 Lashua, L. P., Melvin, J. A., Deslouches, B., Pilewski, J. M., Montelaro, R. C., Bomberger, J. M. (2016)  
 712 Engineered cationic antimicrobial peptide (eCAP) prevents *Pseudomonas aeruginosa* biofilm growth  
 713 on airway epithelial cells. *J. Antimicrob. Chemother.* 71(8):2200-7. doi: 10.1093/jac/dkw143.
- 714 Leitner, L., Ujmajuridze, A., Chanishvili, N., Goderdzishvili, M., Chkonia, I., Rigvava, S. et al. (2021).  
 715 Intravesical bacteriophages for treating urinary tract infections in patients undergoing transurethral  
 716 resection of the prostate: a randomised, placebo-controlled, double-blind clinical trial. *Lancet Infect*  
 717 *Dis.* 21(3):427-436 doi: 10.1016/S1473-3099(20)30330-3.
- 718 Lepak, A. J., Wang, W., Andes, D. R. (2020). Pharmacodynamic Evaluation of MRX-8, a Novel  
 719 Polymyxin, in the Neutropenic Mouse Thigh and Lung Infection Models against Gram-Negative  
 720 Pathogens. *Antimicrob. Agents Chemother.* 64(11):e01517-20. doi: 10.1128/AAC.01517-20.
- 721 Li, J., L. Nation, R., Kaye, K. S. (2019). Polymyxin Antibiotics: From Laboratory Bench to Bedside.  
 722 *Advances in Experimental Medicine and Biology* 1145.
- 723 Liu, B., Trout, R. E. L., Chu, G. H., McGarry, D., Jackson, R. W., Hamrick, J. C. et al. (2020).  
 724 Discovery of taniborbactam (VNRX-5133): a broad-spectrum serine- and metallo- $\beta$ -lactamase

- 725 inhibitor for carbapenem-resistant bacterial infections. *J. Med. Chem.* 63(6):2789-2801. doi:  
726 10.1021/acs.jmedchem.9b01518.
- 727 Lomovskaya, O., Tsivkovski, R., Sun, D., Reddy, R., Totrov, M., Hecker, S. et al. (2021). QPX7728,  
728 An Ultra-Broad-Spectrum B-Lactamase Inhibitor for Intravenous and Oral Therapy: Overview of  
729 Biochemical and Microbiological Characteristics. *Front. Microbiol.* 12:697180. doi:  
730 10.3389/fmicb.2021.697180.
- 731 López-Siles, M., Corral-Lugo, A., McConnell, M. J. (2021). Vaccines for multidrug resistant Gram  
732 negative bacteria: lessons from the past for guiding future success. *FEMS Microbiol. Rev.*  
733 45(3):fuaa054. doi: 10.1093/femsre/fuua054.
- 734 Lu, Q., Rouby, J. J., Laterre, P. F., Eggimann, P., Dugard, A., Giamarellos-Bourboulis, E. J. et al.  
735 (2011). Pharmacokinetics and safety of panobacumab: specific adjunctive immunotherapy in critical  
736 patients with nosocomial *Pseudomonas aeruginosa* O11 pneumonia. *J. Antimicrob. Chemother.*  
737 66(5):1110-6. doi: 10.3390/antibiotics9040155.
- 738 Lucasti, C., Vasile, L., Sandesc, D., Venskutonis, D., McLeroth, P., Lala, M. et al. (2016). Phase 2,  
739 Dose-Ranging Study of Relebactam with Imipenem-Cilastatin in Subjects with Complicated Intra-  
740 abdominal Infection. *Antimicrob Agents Chemother.* 60(10):6234-43. doi: 10.1128/AAC.00633-16.
- 741 MacNair, C. R., Tsai, C. N., Brown, E. D. (2020). Creative targeting of the Gram-negative outer  
742 membrane in antibiotic discovery. *Ann. N. Y. Acad. Sci.* 1459(1):69-85. doi: 10.1111/nyas.14280.
- 743 Martin-Loeches, I., Dale, G. E., Torres, A. (2018). Murepavadin: a new antibiotic class in the pipeline.  
744 *Expert Rev. Anti Infect. Ther.* 16(4):259-268. doi: 10.1080/14787210.2018.1441024.
- 745 Merakou, C., Schaefer, M. M., Priebe, G. P. (2018) Progress Toward the Elusive *Pseudomonas*  
746 *aeruginosa* Vaccine. *Surg. Infect. (Larchmt)* 19(8):757-768. doi: 10.1089/sur.2018.233.
- 747 Micoli, F., Bagnoli, F., Rappuoli, R., Serruto, D. (2021). The role of vaccines in combatting  
748 antimicrobial resistance. *Nat. Rev. Microbiol.* 1–16. doi: 10.1038/s41579-020-00506-3.
- 749 Montravers, P., Yung, S., Tran-Dinh, A. (2020). A spotlight on the treatment of intraabdominal  
750 infections. *Expert Rev. Clin. Pharmacol.* 13(5):469-472. doi: 10.1080/17512433.2020.1766963.
- 751 Moradali, M. F., Ghods, S., Rehm, B. H. (2017). *Pseudomonas aeruginosa* Lifestyle: A Paradigm for  
752 Adaptation, Survival, and Persistence. *Front Cell. Infect. Microbiol.* 7:39. doi:  
753 10.3389/fcimb.2017.00039.
- 754 Motsch, J., Murta de Oliveira, C., Stus, V. et al. (2020). RESTORE-IMI 1: a multicenter, randomized,  
755 double-blind trial comparing efficacy and safety of imipenem/relebactam vs colistin plus imipenem in  
756 patients with imipenem-nonsusceptible bacterial infections. *Clin. Infect. Dis.* 70(9):1799-1808. doi:  
757 10.1093/cid/ciz530.
- 758 Mulcahy, L. R., Isabella, V. M., Lewis, K. (2014). *Pseudomonas aeruginosa* biofilms in disease.  
759 *Microb. Ecol.* 68(1):1-12. doi: 10.1007/s00248-013-0297-x.
- 760 Newman, J. W., Floyd, R. V., Fothergill, J. L. (2017). The contribution of *Pseudomonas aeruginosa*  
761 virulence factors and host factors in the establishment of urinary tract infections. *FEMS Microbiol.*  
762 *Lett.* 364(15). doi: 10.1093/femsle/fnx124.
- 763 Nolan, L. M., Cain, A. K., Clamens, T., Furniss, R. C. D., Manoli, E., Sainz-Polo, M. A., et al. (2021).  
764 Identification of Tse8 as a Type VI secretion system toxin from *Pseudomonas aeruginosa* that targets

- 765 the bacterial transamidosome to inhibit protein synthesis in prey cells. *Nat. Microbiol.* 6(9):1199-1210.  
766 doi: 10.1038/s41564-021-00950-8.
- 767 Pang, Z., Raudonis, R., Glick, B. R., Lin, T. J., Cheng, Z. (2019). Antibiotic resistance in *Pseudomonas*  
768 *aeruginosa*: mechanisms and alternative therapeutic strategies. *Biotechnol. Adv.* 37(1):177-192. doi:  
769 10.1016/j.biotechadv.2018.11.013.
- 770 Patil, A., Banerji, R., Kanojiya, P., Koratkar, S., Saroj, S. (2021). Bacteriophages for ESKAPE: role in  
771 pathogenicity and measures of control. *Expert Rev. Anti. Infect. Ther.* 1-21. doi:  
772 10.1080/14787210.2021.1858800.
- 773 Portsmouth, S., van Veenhuizen, D., Echols, R., Machida, M., Ferreira, J. C. A., Ariyasu, M., Tenke,  
774 P. et al. (2018). Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract  
775 infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-  
776 inferiority trial. *Lancet Infect. Dis.* 18(12):1319-1328. doi: 10.1016/S1473-3099(18)30554-1.
- 777 Powell, L. C., Pritchard, M. F., Ferguson, E. L., Powell, K. A., Patel, S. U., Rye, P. D. et al. (2018).  
778 Targeted disruption of the extracellular polymeric network of *Pseudomonas aeruginosa* biofilms by  
779 alginate oligosaccharides. *NPJ Biofilms Microbiomes* 4:13. doi: 10.1038/s41522-018-0056-3.
- 780 Ramireddy, S., Gudipati, S., Zervos, M. (2020). Expect the Unexpected: A Rare Case of *Pseudomonas*  
781 *aeruginosa* Endocarditis. *IDCases.* 12;21:e00787. doi: 10.1016/j.idcr.2020.e00787.
- 782 Rello, J., Krenn, C. G., Locker, G., Pilger, E., Madl C, Balica L, et al. (2017). A randomized placebo-  
783 controlled phase II study of a *Pseudomonas* vaccine in ventilated ICU patients. *Crit. Care.* 21(1):22.  
784 doi: 10.1186/s13054-017-1601-9.
- 785 Rogan, M. P., Taggart, C. C., Greene, C. M., Murphy, P. G., O'Neill, S. J., McElvaney, N. G. (2004).  
786 Loss of microbicidal activity and increased formation of biofilm due to decreased lactoferrin activity  
787 in patients with cystic fibrosis. *J. Infect. Dis.* 190(7):1245-53. doi: 10.1086/423821.
- 788 Roy, P. H., Tetu, S. G., Larouche, A., Elbourne, L., Tremblay, S., Ren Q. et al. (2010). Complete  
789 genome sequence of the multiresistant taxonomic outlier *Pseudomonas aeruginosa* PA7. *PLoS One.*  
790 2010 Jan 22;5(1):e8842. doi: 10.1371/journal.pone.0008842.
- 791 Ryder, C., Byrd, M., Wozniak, D. J. (2007). Role of polysaccharides in *Pseudomonas aeruginosa*  
792 biofilm development. *Curr. Opin. Microbiol.* 10(6):644-8. doi: 10.1016/j.mib.2007.09.010.
- 793 Sainz-Mejías, M., Jurado-Martín, I., McClean, S. (2020). Understanding *Pseudomonas aeruginosa*-  
794 Host Interactions: The Ongoing Quest for an Efficacious Vaccine. *Cells.* 9(12):2617. doi:  
795 10.3390/cells9122617.
- 796 Salunkhe, P., Smart, C. H., Morgan, J. A., Panagea, S., Walshaw, M. J., Hart, C. A. (2005). A cystic  
797 fibrosis epidemic strain of *Pseudomonas aeruginosa* displays enhanced virulence and antimicrobial  
798 resistance. *J. Bacteriol.* 187(14):4908-20. doi: 10.1128/JB.187.14.4908-4920.2005.
- 799 Sana, T. G., Berni, B., Bleves, S. (2016). The T6SSs of *Pseudomonas aeruginosa* Strain PAO1 and  
800 Their Effectors: Beyond Bacterial-Cell Targeting. *Front. Cell. Infect. Microbiol.* 6:61. doi:  
801 10.3389/fcimb.2016.00061.
- 802 Sato, H., and Frank, D. W. (2011). Multi-Functional Characteristics of the *Pseudomonas aeruginosa*  
803 Type III Needle-Tip Protein, PcrV; Comparison to Orthologs in other Gram-negative Bacteria. *Front.*  
804 *Microbiol.* 2:142. doi: 10.3389/fmicb.2011.00142.

- 805 Sharland, M., Pulcini, C., Harbarth, S., Zeng, M., Gandra, S., Mathur, S. et al. (2018). 21st WHO  
806 Expert Committee on Selection and Use of Essential Medicines. Classifying antibiotics in the WHO  
807 Essential Medicines List for optimal use-be AWaRe. *Lancet Infect. Dis.* 18(1):18-20. doi:  
808 10.1016/S1473-3099(17)30724-7.
- 809 Sheremet, A. B., Zigangirova, N. A., Zayakin, E. S., Luyksaar, S. I., Kapotina, L. N., Nesterenko, L.  
810 N. et al. (2018). Small Molecule Inhibitor of Type Three Secretion System Belonging to a Class 2,4-  
811 disubstituted-4H-[1,3,4]-thiadiazine-5-ones Improves Survival and Decreases Bacterial Loads in an  
812 Airway *Pseudomonas aeruginosa* Infection in Mice. *Biomed. Res. Int.* 2018:5810767. doi:  
813 10.1155/2018/5810767.
- 814 Shrestha, G. S., Vijay, A. K., Stapleton, F., Henriquez, F. L., Carnt, N. (2021). Understanding clinical  
815 and immunological features associated with *Pseudomonas* and *Staphylococcus* keratitis. *Cont. Lens.*  
816 *Anterior Eye* 44(1):3-13. doi: 10.1016/j.clae.2020.11.014.
- 817 Shukla, S. D., Walters, E. H., Simpson, J. L., Keely, S., Wark, P. A. B., O'Toole, R. F. et al. (2020).  
818 Hypoxia-inducible factor and bacterial infections in chronic obstructive pulmonary disease.  
819 *Respirology.* 25(1):53-63. doi: 10.1111/resp.13722.
- 820 Sims, M., Mariyanovski, V., McLeroth, P., Akers, W., Lee, Y. C., Brown, M. L. et al. (2017).  
821 Prospective, randomized, double-blind, Phase 2 dose-ranging study comparing efficacy and safety of  
822 imipenem/cilastatin plus relebactam with imipenem/cilastatin alone in patients with complicated  
823 urinary tract infections. *J. Antimicrob. Chemother.* 72(9):2616-2626. doi: 10.1093/jac/dkx139.
- 824 Smith, J. R., Rybak, J. M., Claeys, K. C. (2020). Imipenem-Cilastatin-Relebactam: A Novel  $\beta$ -Lactam-  
825  $\beta$ -Lactamase Inhibitor Combination for the Treatment of Multidrug-Resistant Gram-Negative  
826 Infections. *Pharmacotherapy* 40(4):343-356. doi: 10.1002/phar.2378.
- 827 Tabor, D. E., Oganessian, V., Keller, A. E., Yu, L., McLaughlin, R. E., Song, E. et al. (2018).  
828 *Pseudomonas aeruginosa* PcrV and Psl, the Molecular Targets of Bispecific Antibody MEDI3902, Are  
829 Conserved Among Diverse Global Clinical Isolates. *J. Infect. Dis.* 218(12):1983-1994. doi:  
830 10.1093/infdis/jiy438.
- 831 Tacconelli, E., Carrara, E., Savoldi, A., Harbarth, S., Mendelson, M., Monnet D. L., et al. (2018). WHO  
832 Pathogens Priority List Working Group. Discovery, research, and development of new antibiotics: the  
833 WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet. Infect. Dis.* 18(3):318-327.  
834 doi: 10.1016/S1473-3099(17)30753-3.
- 835 Thi, M. T. T., Wibowo, D., Rehm, B. H. A. (2020). *Pseudomonas aeruginosa* Biofilms. *Int. J. Mol.*  
836 *Sci.* 21(22):8671. doi: 10.3390/ijms21228671.
- 837 Theuretzbacher, U., Gottwalt, S., Beyer, P., Butler, M., Czaplewski, L., Lienhardt, C. et al. (2019).  
838 Analysis of the clinical antibacterial and antituberculosis pipeline. *Lancet Infect. Dis.* 19(2):e40-  
839 e50. doi: 10.1016/S1473-3099(18)30513-9.
- 840 Theuretzbacher, U., Bush, K., Harbarth, S., Paul, M., Rex, J. H., Tacconelli, E. et al. (2020). Critical  
841 analysis of antibacterial agents in clinical development. *Nat. Rev. Microbiol.* 18(5):286-298. doi:  
842 10.1038/s41579-020-0340-0.
- 843 Theuretzbacher, U., Outterson, K., Engel, A., Karlén, A. (2020). The global preclinical antibacterial  
844 pipeline. *Nat. Rev. Microbiol.* 18(5):275-285.

- 845 Thomas, E. L. and Aune, T. M. (1978). Lactoperoxidase, peroxide, thiocyanate antimicrobial system:  
846 correlation of sulfhydryl oxidation with antimicrobial action. *Infect. Immun.* 20(2):456-63. doi:  
847 10.1086/423821.
- 848 Thomsen, K., Christophersen, L., Bjarnsholt, T., Jensen, P. Ø., Moser, C., Høiby, N. (2016). Anti-  
849 *Pseudomonas aeruginosa* IgY antibodies augment bacterial clearance in a murine pneumonia model.  
850 *J. Cyst. Fibros.* 15(2):171-8. doi: 10.1016/j.jcf.2015.08.002.
- 851 Titov, I., Wunderink, R. G., Roquilly, A., Rodríguez Gonzalez, D., David-Wang, A., Boucher, H. W.  
852 et al. (2020). A Randomized, Double-blind, Multicenter Trial Comparing Efficacy and Safety of  
853 Imipenem/Cilastatin/Relebactam Versus Piperacillin/Tazobactam in Adults With Hospital-acquired or  
854 Ventilator-associated Bacterial Pneumonia (RESTORE-IMI 2 Study). *Clin. Infect. Dis.* 73(11):e4539-  
855 e4548. doi: 10.1093/cid/ciaa803.
- 856 Tse, B. N., Adalja, A. A., Houchens, C., Larsen, J., Inglesby, T. V., Hatchett, R. (2017). Challenges  
857 and Opportunities of Nontraditional Approaches to Treating Bacterial Infections. *Clin. Infect. Dis.*  
858 65(3):495-500. doi: 10.1093/cid/cix320.
- 859 Tümmler, B. (2019). Emerging therapies against infections with *Pseudomonas aeruginosa*. F1000Res.  
860 8:F1000 Faculty Rev-1371. doi: 10.12688/f1000research.19509.1.
- 861 Tunney, M. M., Payne, J. E., McGrath, S.J, Einarsson, G. G., Ingram, R. J., Gilpin, D. F. (2018).  
862 Activity of hypothiocyanite and lactoferrin (ALX-009) against respiratory cystic fibrosis pathogens in  
863 sputum. *J. Antimicrob. Chemother.* 73(12):3391-3397. doi: 10.1093/jac/dky357.
- 864 VanDevanter, D. R. and Chmiel, J. F. (2018). KB001-A, a novel anti-inflammatory, found to be safe  
865 and well-tolerated in cystic fibrosis patients infected with *Pseudomonas aeruginosa*. *J. Cyst. Fibros.*  
866 17(4):484-491. doi: 10.1016/j.jcf.2017.12.006.
- 867 Van Koningsbruggen-Rietschel, S., Davies, J. C., Pressler, T., Fischer, R., MacGregor, G., Donaldson,  
868 S. H. (2020). Inhaled dry powder alginate oligosaccharide in cystic fibrosis: a randomised, double-  
869 blind, placebo-controlled, crossover phase 2b study. *ERJ Open Res.* 6(4):00132-2020. doi:  
870 10.1183/23120541.00132-2020.
- 871 Vieira Colombo, A. P., Magalhães, C. B., Hartenbach, F. A., Martins do Souto, R., Maciel da Silva-  
872 Boghossian, C. (2016). Periodontal-disease-associated biofilm: A reservoir for pathogens of medical  
873 importance. *Microb. Pathog.* 94:27-34. doi: 10.1016/j.micpath.2015.09.009.
- 874 WHO, World Health Organization (2019). 2019 Antibacterial agents in clinical development: an  
875 analysis of the antibacterial clinical development pipeline.  
876 <https://www.who.int/publications/i/item/9789240000193>
- 877 WHO, World Health Organization (2020). 2020 Antibacterial agents in clinical and preclinical  
878 development: an overview and analysis. <https://www.who.int/publications/i/item/9789240021303>
- 879 Wu, D. C., Chan, W. W., Metelitsa, A. I., Fiorillo, L., Lin, A. N. (2011). *Pseudomonas* skin infection:  
880 clinical features, epidemiology, and management. *Am. J. Clin. Dermatol.* 12(3):157-69. doi:  
881 10.2165/11539770-000000000-00000.
- 882 Wunderink, R. G. , Matsunaga, Y., Ariyasu, M., Clevenbergh, P., Echols, R, Kaye, KS, et al. (2021).  
883 Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative

- 884 nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial.  
885 Lancet Infect. Dis. 21(2):213-225. doi: 10.1016/S1473-3099(20)30731-3
- 886 Yaeger, L. N., Coles, V. E., Chan, D. C. K., Burrows, L. L. (2021). How to kill *Pseudomonas*-emerging  
887 therapies for a challenging pathogen. Ann. N. Y. Acad. Sci. 1496(1):59-81. doi: 10.1111/nyas.14596.
- 888 Zhang, Y., Pan, X., Wang L., Chen. L. et al. (2021). Iron metabolism in *Pseudomonas*  
889 *aeruginosa* biofilm and the involved iron-targeted anti-biofilm strategies. J. Drug Target. 29(3):249-  
890 258. doi: 10.1080/1061186X.2020.1824235.
- 891 Zurawski, D. V., McLendon, M. K. (2020). Monoclonal Antibodies as an Antibacterial Approach  
892 Against Bacterial Pathogens. Antibiotics (Basel) 9(4):155.