Supplemental Information

Analysis of the clinical pipeline of treatments for drug resistant bacterial infections: despite progress, more action is needed

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This contribution has been prepared strictly in a personal capacity and reflects the view of the authors. The views expressed must not be attributed to the WHO, its Secretariat, or its Member States.

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**Overview of the drug development process.** Before clinical trials can start, an Investigational New Drug Application (IND) must be submitted and approved by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), Japanese Pharmaceuticals and Medical Devices Agency (PMDA), Chinese National Medical Products Administration (NMPA), CDSCO (Central Drugs Standard Control Organization of the Government of India), Australian Therapeutic Goods Administration (TGA) or equivalent national agency. The antibacterial candidates are then evaluated in a Phase 1 trial or trials to identify the maximum dose that can be administered safely without causing severe side effects. Next, Phase 2 trials are undertaken to further evaluate the dosing regimen and obtain clinical efficacy data. Finally, Phase 3 trial or trials are used to compare the safety and effectiveness of the new antibacterial agents against the current standard treatment. Upon successful completion of Phase 3, a New Drug Application (NDA: FDA, PMDA, NMPA and CDSCO), or a Marketing Authorization Application (MAA: EMA and TGA) must be submitted to a Regulatory Agency, who then decide whether the antibacterial drug is approved for treating patients.

![Structures of compounds with new pharmacophores being developed to treat WHO Priority Pathogens infections](image)

**FIG S1** Structures of compounds with new pharmacophores being developed to treat WHO Priority Pathogens infections
FIG S2 Structures of compounds with new pharmacophores being developed to treat TB and NTM infections

FIG S3 Structures of compounds with new pharmacophores being developed to treat C. difficile infections
| Name (synonym) | Phase | Antibiotic class | Pathogen activity | Developer | Year | Notes and/or reasons for discontinuation |
|----------------|-------|-----------------|------------------|-----------|------|-----------------------------------------|
| GSK-3342830    | 1     | Siderophore-cephalosporin | Gram-ve          | GSK       | 2017 | Adverse event                           |
| AIC-499 + unknown BLI | 1     | β-Lactam + BLI | Gram-ve | AiCuris | 2017 | Unknown                                 |
| DS-2969        | 1     | New class (GyrB inhibitor) | C. difficile | Daiichi Sankyo | 2017 | Adverse event                           |
| 514G3 (omodenbamab) | 1/2   | Anti-S. aureus IgG monoclonal antibody | S. aureus | Xbiotech | 2017 | Study completed in Feb 2017             |
| SQ-109         | 2/3   | Ethanambutol derivative<sup>a</sup> | TB               | Sequela   | 2017 | Unknown                                 |
| SPR-741 + β-lactam | 1     | Polymyxin (potentiator) + β-lactam | Gram-ve | Spero/Everest Medicines | 2018 | Business decision; moving forward with SPR206 |
| Cefilavancin   | 3     | Glycopeptide-cephalosporin hybrid | S. aureus | R Pharm/Theravance | 2018 | Unknown; not in R-Pharm pipeline        |
| Ramoplanin     | 2     | Lipodepsipeptide | C. difficile     | Ology Bioservices | 2018 | Discontinued in Feb 2018               |
| Ancremonam (BOS-228, LYS-228) | 2     | Monobactam | CRE            | Boston Pharmaceuticals | 2018 | Licensed in Oct 2018, but did not move into clinical trials |
| Cadazolid      | 3     | Oxazolidinone-quinolone hybrid | C. difficile | Actelion Pharmaceuticals | 2019 | Discontinued in Mar 2018; Actelion acquired by J&J |
| RC-01 (T 1228) | 1     | New class (LpxC inhibitor) | Gram-ve | Recida/FUJIFILM Toyama | 2019 | Safety                                  |
| GT-1           | 1     | Siderophore-cephalosporin | Gram-ve | Geom     | 2019 | Unknown                                 |
| MK-3866        | 1     | BLI              | Gram-ve | Merck    | 2019 | Business and program changes            |
| Murepavadin (POL7080)<sup>c</sup> | 3     | Peptide          | P. aeruginosa | Polyphor | 2019 | See Footnote 3                          |
| AR-105 (aerucin)<sup>a</sup> | 2     | Anti-P. aeruginosa fully human IgG1 mAb | P. aeruginosa | Aridis (Serum Institute of India) | 2019 | Trial completed in Apr 2019, but not on pipelines |
| BCM-0184       | 1     | Not disclosed (likely peptide) | S. aureus | Biocidium | 2019 | Trial not registered and no update      |
| Iclaprim       | 3     | Trimethoprim     | S. aureus       | Motif     | 2020 | Company ceased operations in Mar 2020   |
| MEDI-3902 (gremubamab) | 2     | Anti-P. aeruginosa IgG mAb | S. aureus | AstraZeneca (Medimmune) | 2020 | Safety/efficacy reasons                 |
| OPS-2071       | 2     | Quinolone        | C. difficile    | Otsuka    | 2020 | Development strategy                    |
| TP-271<sup>a</sup> | 1     | Tetracycline     | S. aureus and S. pneumoniae | La Jolla (Tetraphase) | 2021 | Tetraphase acquired in Jul 2020, La Jolla looking to license |
| TP-6076<sup>a</sup> | 1     | Tetracycline     | A. baumannii   | La Jolla (Tetraphase) | 2021 | Tetraphase acquired in Jul 2020, La Jolla looking to license |

<sup>a</sup> These antibacterials were previously listed as ‘in development’ in the 2020 WHO Pipeline Report.<sup>b</sup> Although SQ-109 is structurally derived from ethambutol, SQ109 has different modes of action that includes inhibition of mMpl3, which is a trehalose monomycolate transporter important in cell wall synthesis (1).<sup>c</sup> The development IV administered murepavadin was discontinued in 2019, but clinical trials are planned to treat P. aeruginosa infections in people with cystic fibrosis using inhaled administration.

Reference: (1) Li W, et al. 2014. Novel insights into the mechanism of inhibition of MmpL3, a target of multiple pharmacophores in Mycobacterium tuberculosis. Antimicrob Agents Chemother 58:6413–6423.