Supplementary Materials

Table S1. Clinically relevant MDR pathogens with the associated infections [7].

Bacteria	No longer functioning Drugs	Infections	Ref.
P. aeruginosa	Aminoglycosides, quinolones β-lactams, carbapenems	Cystic Fibrosis COPD	[8]
Enterococcus spp	β-lactams, aminoglycoside Tetracycline, erythromycin Vancomycin, streptomycin Linezolid, quinolones	Endocarditis, UTI, BSI, IAA, IPA	[9,10]
A. baumannii	β-lactams, tetracyclines Quinolones, polymixins Aminoglycosides Lincosamides Carbapenems	HAP, VAP, UTI Meningitis Bacteraemia, GIT SI, WI	[11]
E. coli	Cephalosporins, fluoroquinolones Levofloxacin, TSX	UTI, BSI	[12]
K. pneumoniae	Cephalosporins, carbapenems	Pneumonia, BSI, UTI	[13]
S. aureus	Methicillin	WI, BSI	[14]
Streptococcus pneumoniae	Penicillin	Pneumonia, meningitis otitis	[15]
Nontyphoidal Salmonella	Fluoroquinolones	Foodborne diarrhea, BSI	[16]
Shigella spp	Fluoroquinolones, ampicillin, TSX Nalidixic acid	Diarrhea *	[17]
Neisseria gonorrhoeae	Cephalosporins, tetracyclines Macrolides, TSX, quinolones.	Gonorrhea	[18]
Mycobacterium tuberculosis	Rifampicin, isoniazid, fluoroquinolone	Tuberculosis	[19]
Fungi			
Candida spp	Fluconazole, echinocandins	Candidiasis	[20]
Cryptococcus neoformans	Fluconazole	Cryptococcosis	[21]
Aspergillus spp	Azoles	Aspergillosis	[22]
Scopulariopsis spp *Onychomycosis*	Amphotericin B, flucytosine, azoles	Onychomycosis	[23]
Virus			
Cytomegalovirus (CMV)	Ganciclovir, foscarnet	AIDS and oncology patients	[24]
Herpes simplex virus (HSV)	Acyclovir, famciclovir, valacyclovir	Herpes simplex	[25]
Human immunodeficiency virus (HIV)	Antiretroviral drugs	AIDS	[26]
Influenza virus	Amantadine, rimantadine Neuraminidase inhibitors	Influenza	[27]
Varicella zoster virus	Acyclovir, valacyclovir	Chicken pox	[25]

Hepatitis B virus (HBV)	Lamivudine	Hepatitis B	[28]
Parasite			
Plasmodia spp	Chloroquine, artemisinin, atovaquone	Malaria	[29]
Leishmania spp	Pentavalent antimonials, miltefosine Paromomycin, amphotericin B	Leishmaniasis	[30,31]
Schistosomes	Praziquantel, oxamniquine	Schistosomiasis	[32,33]
Entamoeba	Metronidazole	Amoebiasis	[34]
Trichomonas vaginalis	Nitroimidazoles	Trichomoniasis	[35]
Toxoplasma gondii	Artemisinin, atovaquone, sulfadiazine	Toxoplasmosis	[36-38]

* Bacillary dysentery; TSX = Trimethoprim-sulfamethoxazole; UTI = urinary tract infection; BSI = bloodstream infection; COPD = chronic obstructive pulmonary disease (COPD); IAA = intra-abdominal abscesses; IPA = intra-pelvic abscesses; HAP = hospital acquired pneumonia; VAP = ventilator-associated pneumonia; GIT = gastrointestinal infections; SI = skin infections; WI = wound infections. The references in the Table are available at the end of the main text at the correspondent numbers.

Table S2. General composition of BFs.

Biofilm Biomass		
Organized communities of pathogens' cells (2-5%)		**Extracellular polymeric substances (EPSs)**
Sessile cells	Persistent cells Dormant cell	Enzymes (polypeptides, 1-60%))
Self-immobilized cells attached to a surface, forming highly coordinated micro-colonies, communicating by the QS system	Small subpopulation of microorganisms reversibly transformed into slowly growing cells	Polysaccharides (40-95%) (Cellulose, PGA, exopolysaccharide)
		Extracellular DNA and RNA (eDNA, eRNA) (1-10%)
		Glycoproteins
		Glycolipids (1-40%) Allow communication between bacteria Stabilize the 3-D structure of BF
		Water (70-97%) (responsible for the flow of nutrients)

PGA = poly-glucosamine.

Table S3. Stages of the BF life cycle.

Stage	Action	Events	Ref.
1	Reversible attachment	Free-floating planktonic cells select a surface for attachment and self-immobilize on it The attachment is not permanent The locomotory tools such as flagella and pili are still maintained	[73]
2	Irreversible attachment	Expression of QS signaling molecules Formation of extracellular polymeric material ⇓ in flagella reversal rates ⇓ in flagella gene expression Cells demonstrate drug tolerance	
3	Grow and cells division (Maturation I)	Recruitment of cells from the environment Appearance of cell clusters * Formation of micro-colonies	
4	Formation of the 3D-structured mature BF (Maturation II)	Expression of genes needed for the mature (3D) extracellular matrix Water-filled channels formation for transport of nutrients and removing waste materials	
5	BF dispersion **	⇓ and degradation of matrix components Detachment of planktonic cells Multiplication and dispersal of motile cells ⇑ Drug susceptibility ***	

* Several cells thick embedded in the BF matrix; ** promoted by QS or enzyme action; *** sometime antibiotic insensitivity can be retained; ⇓ = decrease, reduction; ⇑ = increase. The reference in the Table is available at the end of the main text at the correspondent number.