Proposal from the McMaster Group for a "conserved" antibiotics list – for preservation, niche indications, and last-resort use.

The approach used to develop a list of essential antibiotics was based on infectious syndromes and largely on empirical use, that is, use for suspected infection in the absence of (or pending) microbiological evidence for a specific pathogen. Notable exceptions were endocarditis and bone and joint infections. The concept of a "conserved" list was proposed by the applicant to serve several purposes and the list comprised antibiotics that are positioned here for several different reasons.

One of the most important purposes is *preservation* of certain antibiotics – avoiding their use when there are alternatives that are often safer. In this way, antibiotics proposed for preservation can be kept in reserve until they are really needed for specific circumstances (e.g. patient's intolerance or resistance to core and targeted antibiotics) or for future use when resistance rates to the proposed core and targeted antibiotics are very high. They are thus considered last-resort antibiotics. One example is colistin, which is a polymyxin antibiotic that should be used only for multidrug-resistant organisms, such as extremely multidrug-resistant *Pseudomonas aeruginosa* or *Acinetobacter* spp. Colistin carries a risk of nephrotoxicity and should be used judiciously, that is, under strict medical supervision and only if suitable alternatives are not available. Tigecycline is similar in that it has a relatively broad spectrum of activity, against both Gram-positive and Gram-negative pathogens. However, the FDA issued a boxed warning in 2010 due to concern about an increased risk of death. For this reason, the applicant considered that this should be considered a last-resort antibiotic, to be used only when there is no suitable alternative agent.

Other antibiotics were proposed as "niche" antibiotics in that they should be used only for a narrow range of their clinical uses – niche indications targeting specific resistant pathogens. Linezolid, for example, has broad Gram-positive activity, being active against organisms such as vancomycin-resistant enterococcus (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA). Resistance to linezolid can develop but remains low, which is why this antibiotic should be used selectively. Daptomycin also has excellent Gram-positive activity and should be preserved, given that resistance is currently low. Rifampicin, used for non-tuberculous infection as an adjunct therapy for rifampicin-susceptible staphylococcal prosthetic joint infections and for prosthetic valve endocarditis, is also in this category. Chloramphenicol was included as a niche antibiotic for its role in bacterial meningitis and typhoid fever in settings where alternatives are not available. Ertapenem, a carbapenem with a long half-life, finds a niche for once-daily dosing in the outpatient setting, particularly for coverage of pathogens with a degree of resistance against core and targeted antibiotics, e.g. extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae. In addition to niche indications, ertapenem should be preserved to avoid development of more widespread resistance to carbapenems.

Cefepime, aztreonam and moxifloxacin, were also on the proposed list of preserved antibiotics in order to prevent the development of further resistance. They generally have a reasonable safety profile and good activity: (cefepime, a fourth-generation cephalosporin, has excellent Gram-negative activity; aztreonam has good Gram-negative activity, especially against *Pseudomonas aeruginosa*; and moxifloxacin

has the activity expected of a respiratory fluoroquinolone. However, other antimicrobials offer similar coverage, meaning that these antibiotics could be preserved for use only if existing agents become ineffective.

The table below summarizes the proposals for the conserved antibiotic list from the McMaster Group application

Antibiotic	Systematic reviews	Clinical practice guidelines	Currently listed on EML/EMLc	Proposed list
linezolid	X	√	X	Niche
tigecycline	X	√	X	Last resort
cefepime	X	√	X	Preserved
colistin	X	√	X	Last resort
daptomycin	X	√	X	Niche
moxifloxacin	X	√	X	Preserved
aztreonam	X	√	X	Preserved
rifampicin	X	√	X	Niche
ertapenem	X	√	X	Niche/preserved
chloramphenicol	X	X	√	Niche

Expert Committee considerations and recommendations: the EML Reserve antibiotics group

The Expert Committee considered the various antibiotics proposed in the McMaster application for conservation, and adapted that list to create the EML Reserve antibiotics group, choosing to focus only on "last-resort" antibiotics or antibiotic classes, to be used when all other alternatives have failed. The Reserve group was identified to improve targeted access according to available recommendations and to reduce the risk of selection of resistance to these last-resort antibiotics.

The Expert Committee excluded moxifloxacin and ertapenem from this group, as fluoroquinolones and carbapenems are already included in the Watch group, and meropenem was recommended as a second-choice treatment for a small number of serious infections. Rifampicin and chloramphenicol were not included in the Reserve list as they were not considered by the Expert Committee to fit the definition of last-resort antibiotics.

The Expert Committee considered the Reserve group should include 4th-generation cephalosporins as a class (not just cefepime), as well as 5th-generation cephalosporins. Other antibiotic classes recommended were polymyxins (to include both colistin and polymyxin B), and oxazolidinones (capturing linezolid and others). The Expert Committee also recommended including IV fosfomycin in the Reserve group and agreed that inclusion of aztreonam, tigecycline and daptomycin on the Reserve group was appropriate. The Committee thus listed the antibiotics of the Reserve ("last resort") group as follows:

Reserve group ("last resort") antibiotics

aztreonam
4th-generation cephalosporins, e.g. cefepime
5th-generation cephalosporins, e.g. ceftaroline
Polymyxins, e.g. polymyxin B, colistin
fosfomycin (IV)
Oxazolidinones, e.g. linezolid
tigecycline
daptomycin

The Reserve group antibiotics should be accessible when needed, but their use should be tailored to highly specific patients and settings, when other alternatives have failed (e.g. serious life-threatening infections due to multidrug-resistant bacteria). To preserve their effectiveness, these medicines could be protected and prioritized as key targets of high-intensity national and international stewardship programmes involving monitoring and utilization reporting,.