WHO Essential Medicines List for Antibiotics – adaptation for England

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What is the WHO Essential Medicines List?

• List of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost–effective medicines for priority conditions.

• Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

• List for Adults and Children: core & complementary lists.

• Updated every two years

• Complementary list for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed.
Overhaul of antibacterials list outside of disease-specific subsections of tuberculosis, HIV, hepatitis and malaria

Proposal to split into three groups

- **ACCESS** – first and second choice antibiotics for the empiric treatment of most common infectious syndromes;
- **WATCH** – antibiotics with higher resistance potential whose use as first and second choice treatment should be limited to a small number of syndromes or patient groups; and
- **RESERVE** – antibiotics to be used mainly as ‘last resort’ treatment options.
WHO EML

Access Group:

- those listed as first and second choice for the empiric treatment of the most common infection syndromes
- antibiotics that should be consistently globally widely available at an appropriate quality, dose, duration, formulation and price.
WHO EML – AWaRe Watch Group

- antibiotic classes that were considered generally to have higher toxicity concerns and resistance potential
- Antibiotics were designated to the Watch group to assist the development of tools for stewardship at local, national, and global levels.

WATCH

- Anti-pseudomonal penicillins with beta-lactamase inhibitor (e.g. piperacillin + tazobactam)
- Carbapenems / Penems (e.g. faropenem, imipenem + cilastatin, meropenem)
- Cephalosporins, 3rd Generation (with or without beta-lactamase inhibitor, e.g. cefixime, cefotaxime, ceftazidime, ceftriaxone)
- Glycopeptides (e.g. teicoplanin, vancomycin)
- Macrolides (e.g. azithromycin, clarithromycin, erythromycin)
- Quinolones and fluoroquinolones (e.g. ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin)
WHO EML – AWaRe Reserve group

• Includes new antibiotics and ‘last-resort’ treatment options
• These should be **protected and prioritized as key targets** of high-intensity national and international stewardship programs involving central monitoring and reporting, to **preserve their effectiveness**
Why Reserve? Selection risks associated with antimicrobial classes

<table>
<thead>
<tr>
<th></th>
<th>MRSA</th>
<th>VRE</th>
<th>ESBL</th>
<th>MDR Pseudomonas</th>
<th>C. difficile</th>
<th>Carbapenemases</th>
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<tbody>
<tr>
<td>Carbapenems</td>
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<td>Piperacillin – tazobactam</td>
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<tr>
<td>3rd Gen Cefalosporins</td>
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<td>Quinolones</td>
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<td>Tigecycline</td>
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Other group – antibiotics not listed by WHO EML

• All TB drugs
• Many 1\textsuperscript{st} and 2\textsuperscript{nd} generation cefalosporins including cefaclor, cefoxitin, cefuroxime
• Beta-lactams – temocillin, cofluampicil
• Other aminoglycosides: tobramycin, netilmicin, ticarcillin
• Some tetracyclines (demeclocycline, lymecycline, minocycline)
• UTI agents (trimethoprim, oral fosfomycin, pivmecillinam, methenamine)
• Misc: fusidate, quinupristin-dalfopristin, pristinomycin
English primary care antibiotic use

Antibiotic items per 1000 population by EML category over time

Proportion of antibiotic items per 1000 population by EML category over time

Calendar Year

access access/watch other reserve watch

Calendar Year

access access/watch other reserve watch
Variation in English Primary care antibiotic use

antibiotic items per 1000 population per CCG by EML category

A = access
AW = access/watch
O = other
R = reserve
W = watch
English secondary care antibiotic use

Antibiotic DDDs per 1000 admissions by EML category over time

Proportion of antibiotic DDDs per 1000 admissions by EML category over time
Variation in English Secondary Care

Prescribing in 123 English NHS Acute Trusts in 2016 by EML category

A = access
AW = access/watch
O = other
R = reserve
W = watch
Proportion of W+R in Acute Trusts

- %watch-observe
- %watch
- %reserve
## Key facts about WHO EML applied to England

<table>
<thead>
<tr>
<th>Mean</th>
<th>1.4% (R)</th>
<th>5.0% (W)</th>
<th>21.6% (W-A)</th>
</tr>
</thead>
</table>

- Proportion of trusts with reserve <1% = 70/123
- Proportion of trusts with reserve & watch <5% = 49/123
- Proportion of trusts with reserve & watch <4% = 23/123
- Proportion of trusts with R, W, watch-access <25% = 34/123
- Proportion of trusts with R, W, watch-access <20% = 7/123
How do we adapt the WHO EML for England to reflect current HCAI and AMR priorities?
Refine categories to reflect HCAI & AMR priorities

- Combine **Access—Watch** into **Watch**: azithromycin, clarithromycin, cefixime, ciprofloxacin, vancomycin
- Move 4C antibiotics from **Access** into **Watch**: co-amoxiclav, clindamycin, cefaclor, cefuroxime
- Move carbapenems into **Reserve**
- Move from **Other** to **Access**: trimethoprim, tetracycline, fosfomycin oral, pivmecillinam, fusidate
- Move from **Other** to **Watch**: all cefalosporins & fluoroquinolones, acne tetracyclines, pristinamycin (ULM), tobramycin (CF use)
Adapted EML list applied to hospitals (excluding other)

Proportion of DDD per 1000 admissions

Year

2011
2012
2013
2014
2015
2016

Proportion

0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%

watch
reserve
access
How do we apply the adapted WHO EML into practice in England?

• Primary care already focuses on reducing most antibiotics in *Watch* group (cefalosporins, fluoroquinolones and co-amoxiclav) to below 10% of all prescriptions. Currently 8.9%

• Hospitals AMR CQUIN has focused on reducing total, carbapenems & piperacillin-tazobactam per admission (AMS)
  – piperacillin-taz shortage changed many empiric antibiotic policies
  – Despite pip-tazo being available again, not all have changed back. FY1718 use 43% less BUT extra £14m spend. Total impact £31m↑
  – Replaced by: co-amoxiclav IV (1.7%↑ of IV AB share), cefuroxime 1.4%↑, amoxicillin 1.1%↑, ceftriaxone 0.6%↑, metronidazole 0.4%↑, ceftazidime, ciprofloxacin, levofloxacin, temocillin, teicoplanin 0.3%↑
<table>
<thead>
<tr>
<th>Access</th>
<th>Watch</th>
<th>Reserve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin / ampicillin Penicillin – all forms</td>
<td>Amikacin, tobramycin, etc Macrolides</td>
<td>Aztreonam</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>Macrolides</td>
<td>Ceftobiprole,</td>
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<tr>
<td>Doxycycline</td>
<td>Most cefalosporins</td>
<td>Ceftaroline</td>
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<tr>
<td>Flucloxacillin</td>
<td>Chloramphenicol</td>
<td>Ceftazidime-avibactam</td>
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<tr>
<td>Fosfomycin oral</td>
<td>Fluoroquinolones</td>
<td>Ceftolozane-tazobactam</td>
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<td>Fusidate</td>
<td>Clindamycin</td>
<td>Colistin</td>
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<tr>
<td>Gentamicin</td>
<td>Co-amoxiclav</td>
<td>Daptomycin</td>
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<tr>
<td>Metronidazole</td>
<td>Other tetracyclines</td>
<td>Carbapenems</td>
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<tr>
<td>Nitrofurantoin</td>
<td>Fidaxomicin</td>
<td>Fosfomycin IV</td>
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<td>Pivmecillinam</td>
<td>Piperacillin-tazobactam, etc</td>
<td>Linezolid / tedizolid</td>
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<tr>
<td>Tetracycline</td>
<td>Temocillin</td>
<td>Televancin</td>
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<tr>
<td>Trimethoprim</td>
<td>Vancomycin, teicoplanin</td>
<td>Tigecycline</td>
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**Adapted WHO EML AWaRe List for England**
Will AWaRe element in serious infections CQUIN put pressure on supply chain by increasing access AB by 3% or to 55%+?

Mean 53% access
Trusts at 55% already = 33/142 (23%)
Trusts with <3% target = 21/142 (15%)
Trusts with 3% target = 88/142 (62%)

- Might impact on supply chain where pressure already eg IV co-trimoxazole, IV gentamicin, IV metronidazole
- But, might take pressure off other “pinch” areas eg IV pip-tazo, IV chloramphenicol, IV amikacin, IV clindamycin
Are there any areas of contention or benefit that need further review?

• Co-trimoxazole – black triangle drug. Move to Watch? No

• ULM might grow eg IV doxycycline

• Financial benefit of using access drugs (see right)
Feedback on Access group

Table: Access

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<td>Pivmecillinam</td>
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<tr>
<td>Tetracycline</td>
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<tr>
<td>Trimethoprim</td>
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Numerous supply restrictions means that consumption of gentamicin & co-trimoxazole cannot be increased. Need to monitor closely.

Should methenamine be added to the list? No – limited evidence base

Oxytetracycline & demeclocycline in the “other tetracycline” list in watch list. Should they be in access list? All except doxycycline into Watch list as mainly used for acne.

CQUIN queries with AWaRe categories
Fidaxomicin – narrow spectrum, 1st/2nd line Tx in IDSA guideline, but not PHE yet. ↓ mortality & Cdiff recurrence. Move to Access? **No**

Temocillin – narrow spectrum penicillin, reliable supply chain, carbapenem sparing, lower C.diff risk. Would Temocillin be suitable for the Access group? **No - in Watch in France & ESBL cover.**

Vancomycin & Teicoplanin – used in pen allergy. Does this include oral Vancomycin? **Yes. Driver to ↓ inappropriate allergy label?**

**Watch**
- Amikacin, tobramycin, etc
- Macrolides
- Most cefalosporins
- Chloramphenicol
- Fluoroquinolones
- Clindamycin
- Co-amoxiclav
- Other tetracyclines
- Fidaxomicin
- Piperacillin-tazobactam, etc
- Temocillin
- Vancomycin, teicoplanin

CQUIN queries with AWaRe categories
Challenges to Reserve group

Should quinupristin & dalfopristin be added here?
Minimal use but probably

Should dalbavancin & oritavancin be added here?
Yes – despite dalbavancin offering an OPAT alternative

Paediatric centres will struggle to use Access antibiotics due to licencing, formulations and palatability, so exclude from CQUIN element?

Reserve

Aztreonam
Ceftobiprole, Ceftaroline
Ceftazidime-avibactam
Ceftolozane-tazobactam
Colistin
Daptomycin
Carbapenems
Fosfomycin IV
Linezolid / tedizolid
Televancin
Tigecycline
Will I need to change all of my empiric guidelines?

- Good **antibiotic stewardship** should naturally decrease proportion of many watch and reserve antibiotics.
- Currently **no evidence** that trusts with greater access proportions have higher total antibacterial (J01) use per admission, or less *C. difficile* rates, but significantly lower carbapenem use (impact of specialist trusts)

\[ R^2 = 0.01 \]

\[ R^2 = 0 \]

\[ R^2 = 0.17 \]
Are there any tools available to help?

- RX-info Define have developed standard reporting tools to show split by adapted WHO EML type: Antimicrobial prescribing – antibacterials
  - RMOC - Proportion of DDD per 1000 admissions by EML (England) category over last 12 months
  - RMOC - Box and whisker distribution of regional EML (England) category over last 12 months
  - RMOC - Trend in use of DDD per 1000 admissions by EML (England) category over last 12 months

Yorks & Humber
AWaRe for last 12 months
- 4 trusts >55% Access
- Mean 48% Access (32-63%)
Does adapted EML AWaRe vary by Trust type?

<table>
<thead>
<tr>
<th>Trust Type</th>
<th>Access</th>
<th>Watch</th>
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<tbody>
<tr>
<td></td>
<td>45%</td>
<td>50%</td>
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<td></td>
<td>49%</td>
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<tr>
<td></td>
<td>46%</td>
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<td>51%</td>
<td>46%</td>
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<tr>
<td></td>
<td>33%</td>
<td>53%</td>
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Summary of adapted WHO EML AWaRe list

• WHO Essential Medicines Lists those medicines needed for basic medical care based on most efficacious, safe and cost-effectiveness for most common conditions

• Major revision of antibacterials in 2017 and categorised them into Access, Watch, Reserve and Other (AWaRe)
  – Access – 1\textsuperscript{st} & 2\textsuperscript{nd} line choice for empiric treatment
  – Watch – higher AMR potential
  – Reserve – last line antibiotics for MDR infections

• List adapted to reflect UK HCAI and AMR policy

• CQUIN incentive to \(\uparrow\) access proportion by 3% or to 55%+
Thanks to Dr Susan Hopkins & Dr Emma Budd for providing the English primary and secondary care antibiotic prescribing data by EML “AWARE” category
Any questions?

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