Update on the WHO EML 2017 process: focus on the selection of antibiotics

IPC Seminar,
Geneva – 9th December 2016

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Geneva, 17–21 October 1977

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19th EML & 5th EMLc - 2015

- 19th EML: **409** medicines
  - 5th EMLc (children): **294** medicines

586 pages, 1082 references
WHO Adds Gilead Hepatitis C Drugs to Its List of Essential Medicines

By ED SILVERMAN

As the debate over the cost of prescription drugs accelerates, the World Health Organization has added several treatments for cancer and hepatitis C to its list of so-called essential medicines, which the agency believes should be made available at affordable prices.

The move comes amid growing friction between payers – both public and private – and the pharmaceutical industry over drug pricing. The addition of the WHO follows requests by consumer groups for the agency to widen its list to include some of the latest treatments carrying high price tags.

Among the drugs added to the list are three hepatitis C treatments – Sovyat and Harvoni, which are sold by Gilead Sciences, and the Vertex PAK medication sold by AbbVie.

WHO adds Hepatitis C drugs in the list of essential medicines

By Karla Petrow - May 9, 2015

Pricey new hepatitis C and cancer drugs make Essential Medicines List

The World Health Organization (WHO) logo is pictured at the entrance of its headquarters in Geneva, January 28, 2015. The World Health Organization has added new curative treatments for hepatitis C to its essential medicines list, but the U.N. agency said prices needed to fall to make them accessible to poorer countries.

The treatment of hepatitis C, which affects about 150 million people globally and kills around half a million each year, has been transformed by the arrival of new drugs, such as Gilead's Sovaldi.

These products can cure hepatitis C but are out of reach at Western prices to patients in poorer countries.
EML 1977: early evidence-based adopter

- Important medicines for:
  - Antibiotics
  - Neglected diseases
  - Pain
  - Mental health
  - Chronic diseases
  - Cancer

- Concise and clear

- Promoting uptake of best research findings on medicines into healthcare and national policies

No medicines for:

- Memory loss and dementia
- Hepatoprotectants
- Immunostimulants
- Osteoporosis
- Medicines for dubious conditions (disease mongering)

- No medicines listed subsequently withdrawn for unexpected risks (e.g., cox-2 inhibitors)
Essential Medicines

Guiding principle: A limited range of carefully selected medicines leads to better health care, better medicines management, and lower costs

Definition: Essential medicines are those that satisfy the priority health care needs of the population

Selection: Selected with due regard to disease prevalence, evidence on efficacy and safety, and comparative cost-effectiveness
EML criteria (EB 109/8, 2001)

- Disease burden and public health need/relevance
- Sound and adequate data on the efficacy (on relevant outcomes), safety and comparative cost-effectiveness
  - “Absolute cost of the treatment will not constitute a reason to exclude a medicine from the Model List that otherwise meets the stated selected criteria”
  - “Affordability changed from a precondition into a consequence of the selection” (Hogerzeil, BMJ, 2004)
- WHO responsible management and oversight of Cols
- 2008 WHO new Guideline Manual, adopting GRADE
- Other considerations: availability, guidelines
Essential medicines are still essential

On Oct 21, WHO published the full report of the 20th Expert Committee on the Selection and Use of Essential Medicines, with its new WHO Model List of Essential Medicines (EML). The new list includes recently developed medicines for drug-resistant tuberculosis (bedaquiline and delamanid), a number of new cancer treatments (such as imatinib, rituximab, and trastuzumab), and, perhaps most controversially, new direct-acting antiviral drugs (DAA) for the treatment of hepatitis C (sofosbuvir, simeprevir, daclatasvir, ledipasvir, and ombitasvir). Several of these medicines are very expensive. For example, the new medicines to treat hepatitis C are priced up to US$95 000 per 12-week course of treatment, and their primary patents will only expire in 2024–30. Despite the ability of some payers and intermediaries to negotiate large discounts, even high-income countries are struggling to pay for broad access to these treatments.

For many years, the WHO Model List has been viewed by some as applicable only to resource-constrained settings, and was assumed to include only the most basic medicines. This is a profound misunderstanding. The same principle of a limited list of cost-effective services underpins the logic of managed care institutions, hospital formularies, and reimbursement lists. The idea of selecting a limited list of essential medicines applies in all countries and in a variety of settings.

We therefore believe that the inclusion of the newly listed cancer treatments, as well as the much-needed options for drug-resistant tuberculosis, is consistent with the definition of essential medicines. In 2002, WHO decided that cost alone would not prevent a medicine from being listed, if other criteria of safety, efficacy, and comparative cost-effectiveness were fulfilled. Yet the 2015 decision to include a range
EML 2015: 77 applications and a few big challenges

- Cancer drugs: a large comprehensive review was commissioned (29 applications)
- New highly effective HCV drugs (new direct antiviral, single agents and combinations, IFN free regimens)
- MDR-TB drugs (4) and 1 for TB prophylaxis
- Rejections: New oral anticoagulants (NOACs), polypill, ranibizumab
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# EML AB review

| 2. Pharyngitis | 11. Skin and soft tissue infections (including cellulitis and surgical site infections) |
| 4. Otitis media | 13. Sexually transmitted diseases (STDs) / urethritis |
| 5. Urinary tract infections | 14. Exacerbations of chronic obstructive pulmonary disease (COPD) |
| 7. Hospital acquired pneumonia (HAP) and ventilator associated pneumonia (VAP) | 16. Infections in immunocompromised hosts |
| 8. Endocarditis |  |
EML AB review: CAP the template

- Intro/background
- Pathogens
- SRs
- GLs
- Proposed listing: core vs targeted
## EML AB review: CAP the template

**Antibiotics selected as essential for CAP:**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Adults</th>
<th>Paediatrics</th>
<th>SR*</th>
<th>CPG</th>
<th>EML</th>
<th>List</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin +/- clavulanate</td>
<td>1g PO</td>
<td>30mg/kg</td>
<td>✓</td>
<td>✓</td>
<td>+</td>
<td>C</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>1g/62.5mg PO</td>
<td>see above</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>500mg PO</td>
<td>7.5mg/kg</td>
<td>✓</td>
<td>✓</td>
<td>+</td>
<td>T</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>50mg/kg IV</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>+</td>
<td>T</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>3.375g IV</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>+</td>
<td>T</td>
</tr>
<tr>
<td>Cefotaxime or ceftriaxone</td>
<td>1g IV</td>
<td>50mg/kg 75-100mg/kg</td>
<td>✓</td>
<td>✓</td>
<td>+</td>
<td>T</td>
</tr>
<tr>
<td>Cefazdime</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>750mg PO/IV</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>+</td>
<td>T</td>
</tr>
<tr>
<td></td>
<td>400mg PO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100mg PO</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>+</td>
<td>T</td>
</tr>
<tr>
<td>Gentamicin</td>
<td></td>
<td>2.5mg/kg IV</td>
<td>✓</td>
<td>✓</td>
<td>+</td>
<td>T</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>15-20mg/kg IV</td>
<td>10-20mg/kg IV</td>
<td>✓</td>
<td>✓</td>
<td>+</td>
<td>T</td>
</tr>
</tbody>
</table>

Recommended duration is at least 5 days, and assessment of an extension of the duration is based on the clinical assessment.
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EML AB children reviews

- In addition to the 20 syndromes (adult and children), 5 syndromes were reviewed in greater detail:
  - Sepsis (neonates)
  - CAP
  - Severe/bloody diarrhea
  - Severe malnutrition

Additional questions addressed:
- Quinolones role in diarrhea
- Interaction between quinolones and artemisinin-based malaria treatments (for QT prolongation)
11. CONCLUSIONS

- The current WHO guidelines supporting the use of fluoroquinolones (first line), beta-lactams (second-line) and cephalosporins (second-line) accord with the currently available evidence and other international guidelines – there is no strong reason to change this guidance.

- Azithromycin is currently listed in WHO guidelines as a second-line therapy for adults with Shigellosis and as first-line for children in other guidelines. Due to evidence of increasing resistance worldwide and the uncertain potential to cause cardiac conduction problems when co-administered with other CYP3A4 inducing drugs, we do not recommend upgrading this medication to a first-line therapy without further trial evidence of clinical efficacy and safety for children. **Listing azithromycin as a second-line therapy may be appropriate for regions with known high-rates of ciprofloxacin non-susceptibility.**

- While there is very limited evidence to suggest azithromycin is associated with an increased risk of cardiac arrhythmias in paediatric patients, this has been documented in adult populations with underlying cardiovascular risk factors in high-income settings. However, research suggests...
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Characteristics and outcomes of public campaigns aimed at improving the use of antibiotics in outpatients in high-income countries

Benedikt Huttner, Herman Goossens, Theo Verheij, Stephan Harbarth, on behalf of the CHAMP consortium

The worldwide increase in resistance to antimicrobial drugs has made reducing the unnecessary use of antibiotics a public health priority. There have been campaigns in many countries to educate the public about appropriate use of antibiotics in outpatients. By use of a comprehensive search strategy and structured interviews, we were able to identify and review the characteristics and outcomes of 22 campaigns done at a national or regional level in high-income countries between 1990 and 2007. The intensity of the campaigns varied widely, from simple internet to expensive mass-media campaigns. All but one campaign targeted the public and physicians simultaneously. Most campaigns that were formally evaluated seemed to reduce antibiotic use. The effect on resistance to antimicrobial drugs cannot be assessed accurately at present. Although the most effective interventions and potential adverse outcomes remain unclear, public campaigns can probably contribute to more careful use of antibiotics in outpatients, at least in high-prescribing countries.

Introduction
Resistance to antimicrobial drugs is an increasing threat to public health. The reasons for the increase in antimicrobial resistance are complex, but it has become evident that excessive use of antibiotics is linked to the emergence and selection of resistance. In high-income countries the majority of antibiotics for use in human

Geographic distribution
Applying our search and selection criteria, we were able to identify 22 campaigns (table 1). Campaigns were done on a national and six on a regional level. In the USA, the CDC’s Get Smart programme is mostly done at the state level and comprises more than 30 different regional campaigns (table 1 includes a selection of the more
The New Antibiotic Mantra—"Shorter Is Better"

Brad Spellberg, MD

In AD 321, Roman Emperor Constantine the Great codified that there would be 7 days in a week. Even in the modern era of evidence-based-medicine, this 1695-year-old decree remains a primary reference for duration of antibiotic therapy: it leads physicians to treat infections in intervals of 7 days. Thus, it is gratifying when clinical trials challenge the standard antibiotic duration of 7 to 14 days.

In the past, community-acquired pneumonia was treated with a 7- to 14-day course of antibiotics. However, clinical trials in the early 2000s demonstrated that 3 or 5 days of protocol-specified antibiotics are as efficacious as longer courses of therapy for patients with mild to moderately severe community-acquired biotic therapy is at least as effective as 10 days for the treatment of community-acquired pneumonia.3

In his keynote address at an annual meeting of the Infectious Diseases Society of America, Louis B. Rice, MD, pointed out that pneumonia was successfully treated with short durations of antibiotics as long ago as the 1940s.4 Physicians considered “pioneers” of penicillin customized the duration of therapy depending on the patient’s response and found that a range of 1½ to 4 days of therapy resulted in high cure rates. The modern concept that we should continue treating bacterial infections past the time when signs and symptoms have resolved can be traced to 1945. Meads et al wrote that they administered penicillin to patients with pneumonia. “until there
On AB duration and resistance

• The modern concept that we should continue treating bacterial infections past the time when signs and symptoms have resolved can be traced to 1945.

• Meads et al wrote that they administered penicillin to patients with pneumonia, “until there was definite clinical improvement and the temperature had remained below 100°F for 12 hours...then given for another two to three days.” 5(p748)

• The perceived need to treat beyond resolution of symptoms was driven by a desire to prevent relapses. However, the recurrent infections seen in the case series were caused by isolates with distinct bacterial serotypes, indicative of reinfection rather than relapse. It is unclear how this confused desire to prevent reinfections subsequently transformed into the illogical dogma that antibiotic resistance could be prevented by continuing therapy beyond resolution of symptoms. 4
On AB duration and resistance

• Nevertheless, this dogma has been reinforced by the equally illogical, often-heard statement that to prevent anti-biotic resistance, it is necessary for patients to complete the entire prescribed course of therapy, even after resolution of symptoms.

• There is no evidence that taking antibiotics beyond the point at which a patient’s symptoms are resolved reduces antibiotic resistance.

• To the contrary, specifically for pneumonia, studies have shown that longer courses of therapy result in more emergence of antibiotic resistance, which is consistent with everything we know about natural selection, the driver of antibiotic resistance.

• Thus, all that is achieved by treating an infection with antibiotics for longer than the patient has symptoms is increased selective pressure driving antibiotic resistance among our colonizing microbial flora.
EML AB: policy recommendations

- For public awareness campaign on AMR:
  - What are the key messages and the evidence supporting them

- For stewardship programs:
  - What works and what doesn’t
  - Big issue of implementation and knowledge gap for different contexts
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**AB EML listing: a 3 by 3 approach?**

<table>
<thead>
<tr>
<th>Level 1</th>
<th>Antibiotics that are first line choice for empirical therapy (e.g., penicillin G, amoxicillin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core/Standard</td>
<td></td>
</tr>
<tr>
<td>Level 2</td>
<td>Antibiotics whose use should be limited to specific subgroups or target populations: patients with penicillin allergy, more severe disease, defined resistance, ...</td>
</tr>
<tr>
<td>Targeted/Specific</td>
<td></td>
</tr>
<tr>
<td>Level 3</td>
<td>“Niche” - Antibiotics whose use should be limited to special “niche” indications (e.g. azithromycin in sexually transmitted diseases)</td>
</tr>
<tr>
<td>Restricted access</td>
<td>“Preserved” - Antibiotics that should be preserved and recommended only in limited, specific circumstances (e.g., linezolid for hospital-acquired MRSA pneumonia)</td>
</tr>
<tr>
<td></td>
<td>“Last resort” - Antibiotics whose use should be strictly preserved and “last resort”, (e.g., colistin for multi-drug resistant hospital-acquired infections)</td>
</tr>
</tbody>
</table>
Public Awareness Campaigns:
- Key messages
- Privilege contents based on evidence

EML AB strategy 2017

1. EML AB listing (3+3)
2. Syndromes guidances
   Comprehensive Review of optimal use
   5 Paediatric Syndromes and specific indications

3. Stewardship & Education & audit
   WHO package based on new EML and 20 syndromes guidances

4. Implementation:
   context dependent and research oriented
   Health System programs: monitoring

5. Priority Pathogens List - R&D

7. Research Priorities & GARDP new AB

8. Essential Diagnostics

9. Drug Utilization
   - Hospital pps
   - Community use
   - Across sectors (animals and agriculture)

10. Animals & Agriculture One Health
    - CIA List (EML bridges)

New EML website:
- based on ideas bed
- New App?
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EML 2017: 85 applications

- AB chapter review
- Cancer
- HepC, HIV, TB, Malaria
- CV: polypill, NOACs, ARBs, combinations ACE-I+thiaz
- Deletions requested for: oseltamivir, bevacizumab

- All application will be published on WHO EML website by 15 January 2017
From the Lancet Commission on EML

- These five core challenges for essential medicines policies are not new. Indeed, over the past few decades the global health community has sought to address them at all levels.

- However, finding long-lasting sustainable solutions has proved difficult. National and global economic and political interests have strongly influenced the development and implementation of essential medicines policies, which have implications for public health, economic development, and trade.

- As a result, essential medicines policies are often highly contested, at both national and global levels.

- (five challenges: adequate financing, affordability, quality and safety, rational/appropriate/optimal use, missing and research)
Simultaneously, although these policies affect the prevention and treatment of many diseases, essential medicines are rarely presented at the centre of the global health agenda.

Instead, all too often essential medicines policies are incorrectly regarded as a technical side issue for which answers are known and easily applied.

In this report, the Commission argues that essential medicines pose a central challenge to the sustainable development agenda, demanding creative and bold action. As an example, the Commission presents the case of new essential medicines for treating hepatitis C (panel 2). This case illustrates that essential medicines policies are relevant for all countries regardless of income level, and that the five challenges are closely related.

(five challenges: adequate financing, affordability, quality and safety, rational/appropriate/optimal use, missing and research)
The need for an investment:
EML presentation
dissemination-adaptation-implementation

Guiding principle:
separating evidence from recommendations
INFORMATION DIVIDED IN 2 COMPONENTS

EVIDENCE

derived from

- GRADE tables (WHO)
- Systematic reviews (WHO)
- External (e.g., Cochrane)

RECOMMENDATIONS

derived from

- Guidelines (WHO)
- TRS (WHO)
- Policy documents (WHO)

EVIDENCE → DECISIONS
Essential Medicines List: Concept and Procedures

EML explorer - website

Search..

World Health Organization

Prev  > EML00355  Sofosbuvir  Tablet; 400 mg

BASICS

Complementary list

Advanced

Process: largely manual

- Metastatic breast cancer: the overall hazard ratios for overall survival and progression-free survival were 0.82 and 0.61 respectively.
- Use of
  - forest plots
  - summary of findings tables
  - graphs (e.g. survival curves)
- Recommendations:
  - WHO recommends that delamanid may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB (conditional recommendation; very low confidence in estimates of effect).
- Prices of medicines
  - Seroprevalence by region
  - Case definition
  - Country programs