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World Health Organization's Essential Medicines List: From Idea to Implementation

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Global Health Education Consortium
and collaborating partners

Objectives

At the end of this presentation, the reader will be able to...

- Analyze the rationale for the creation of the World Health Organization (WHO) Essential Medicines List.
- Identify how and why a medication is added to the WHO Essential Medicines List.
- Assess the current utility of the WHO Essential Medicines List in developing countries.
- Describe the barriers to implementation of the WHO Essential Medicines List in developing countries.

WHO Definition of Health

- WHO Constitution states: “Health is a state of complete physical, mental and social well-being and not merely an absence of disease or infirmity.”
- Definition of health reaffirmed in the Alma-Ata Declaration (1978) and specifically stated:
 - Primary health includes: at least...provision of essential drugs

Medicines



<http://www.indopia.in/resources/images/original/medicines.jpg>

Defining Essential Medicines

- Original definition (1977) “of utmost importance, basic, indispensable, and necessary for the healthcare needs of the population”
- Current definition (2002) “Essential medicines are those that satisfy the priority health care needs of the population”

http://www.who.int/topics/essential_medicines/en/

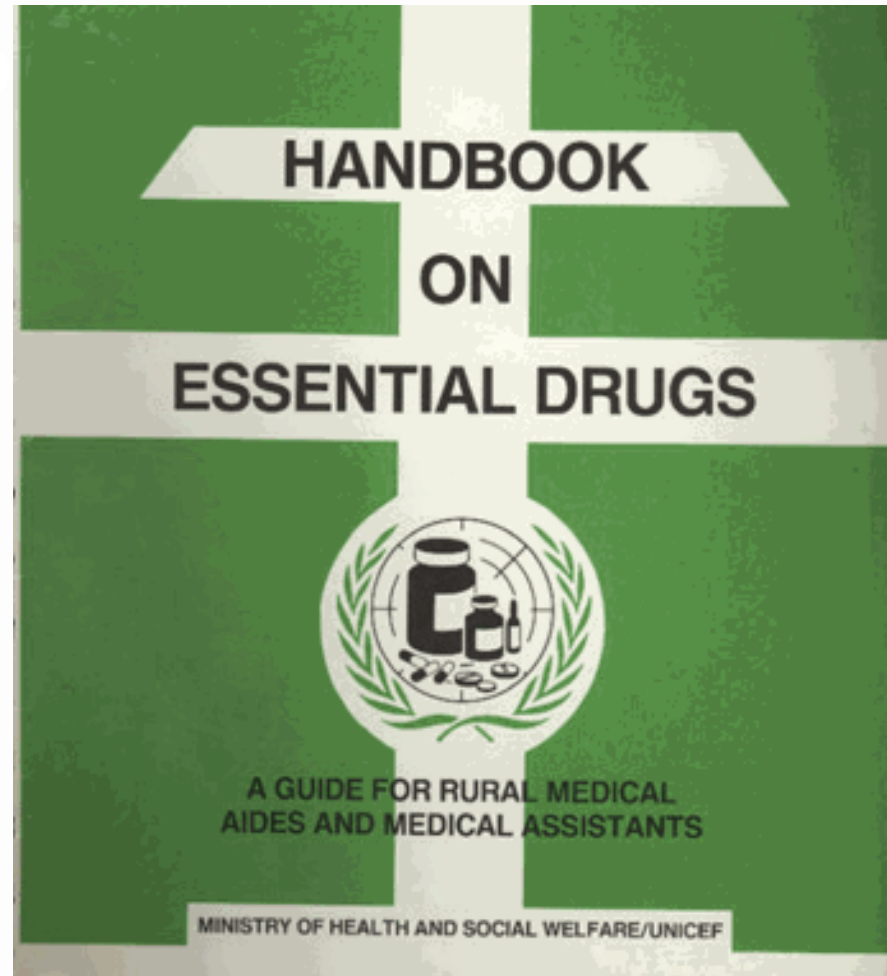
Notes on Defining Essential Medicines. The full definition of essential medicines is given below. The main point of this definition is to reinforce that the list is not a permanent list of must have medicines but rather a guide. Each country must determine its own list based on the current and future public health needs, and availability of medicines.

Essential medicines are those that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford. The implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations; exactly which medicines are regarded as essential remains a national responsibility

History of Essential Medicines

- 1975 World Health Assembly (WHA) meeting, report by WHO Director-General regarding problems facing countries in area of medicines, first mention of essential medicines
- 1977 first Expert Committee on essential medicines issues technical report and compilation of essential medicines
- 1978 Resolution WHA 31.32 passed urging members to establish national essential medicine lists
- 1978 Alma-Ata Declaration on primary care issued

Handbo



What is the “List”?

- There are 2 components
 - Core list is the minimum for a basic health care system
 - Complementary list covers priority diseases that require special facilities, equipment, and/or training
- Divided into therapeutic categories

Core List Medicines

- Treat priority conditions – current or future public health issues with potential for safe and cost-effective treatment

Based upon:

- Efficacy
- Safety
- Cost-effectiveness

Complementary List Medicines

- Treat a priority condition
- Require special:
 - Diagnostic or monitoring facilities
 - Medical care
 - Training
- Consistently higher cost or minimal cost-effectiveness

Therapeutic Equivalence

- Similar clinical performance within a pharmacological class
- Listed medicine should be an example of the therapeutic class
 - May have best evidence for efficacy and safety
 - May be first licensed compound
 - When no difference in efficacy or safety between agents, may be least expensive option

WHO Model List of Essential Medicines 15th List March 2007

Therapeutic equivalence indicates that medicines have similar clinical efficacy, though there may be some benefits of one medicine over another based on dosing frequency or side effect profile. In the U.S. the most common example of drugs with therapeutic equivalence are the HMG-CoA Reductase Inhibitors or “Statins” (e.g. Rosuvastatin, atorvastatin, simvastatin, lovastatin, pravastatin)

Example

Core Medicine

1.2 Local anesthetics	
<input type="checkbox"/> bupivacaine	Injection: 0.25%; 0.5% (HCl) in vial
<i>ephedrine</i>	Injection: 30mg (HCl)/mL in 1-mL ampule <i>(Spinal anesthesia during delivery, prevent hypotension)</i>

Indicates multiple Therapeutic Equivalent agents
(e.g. Ropivacaine, Mepivacaine, Levobupivacaine)

Complementary Medicine

Updating the List

- Updated every 2 years by expert committee
- New medicines or updates are submitted via application
- Expert committee reviews applications and available data and recommend medicines to add

http://www.who.int/topics/essential_medicines/en/

Medicine Applications: Additions, Updates or Deletions

- Application submitted or supported by a WHO group
- Organizations consulted and/or supporting the application
- Public health relevance of drug
- Includes **comparative** efficacy, safety and cost-effectiveness
- International availability (manufacturers)
- Regulatory status (in country of origin and abroad)
- Availability of pharmacopoeia standards (USP)

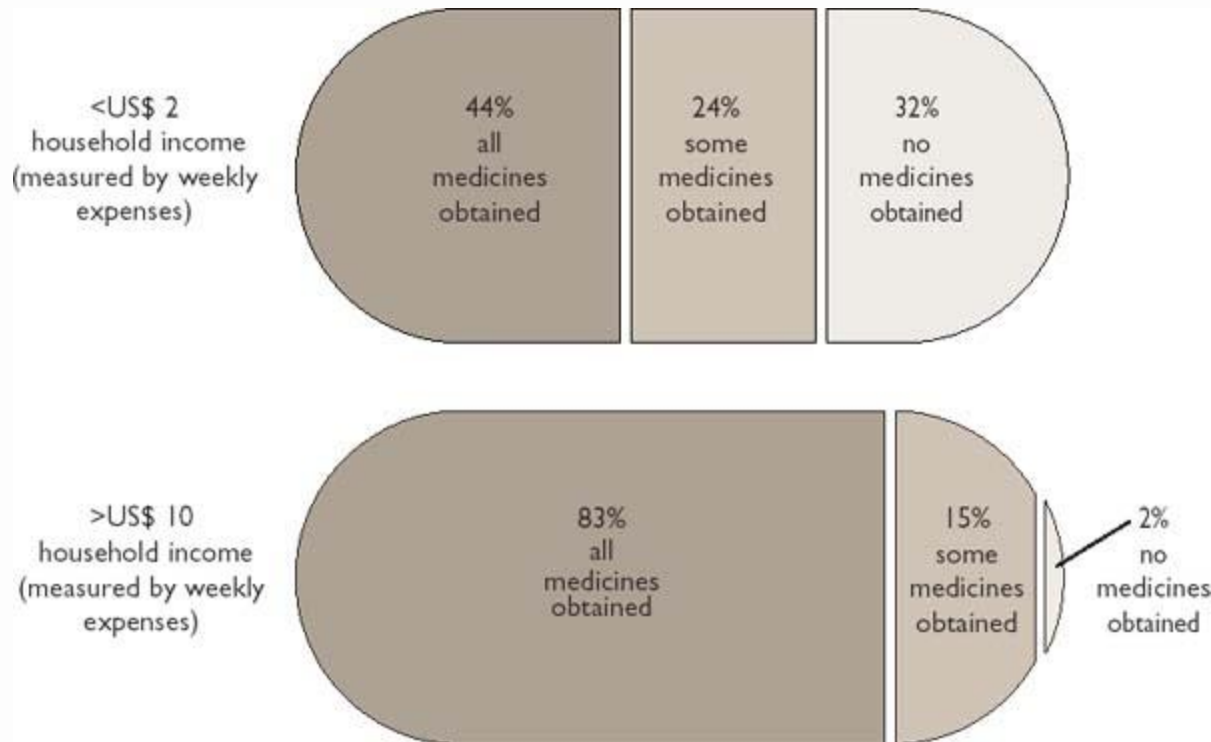


Reasons For the List

- Portion of health dollars spent on pharmaceuticals
 - Developed countries 20%
 - Transitional countries 15-30%
 - Developing countries 25-66%
- Pharmaceuticals are largest public expenditure on health after personnel costs in low income countries

http://www.who.int/topics/essential_medicines/en/

Medicine Affordability



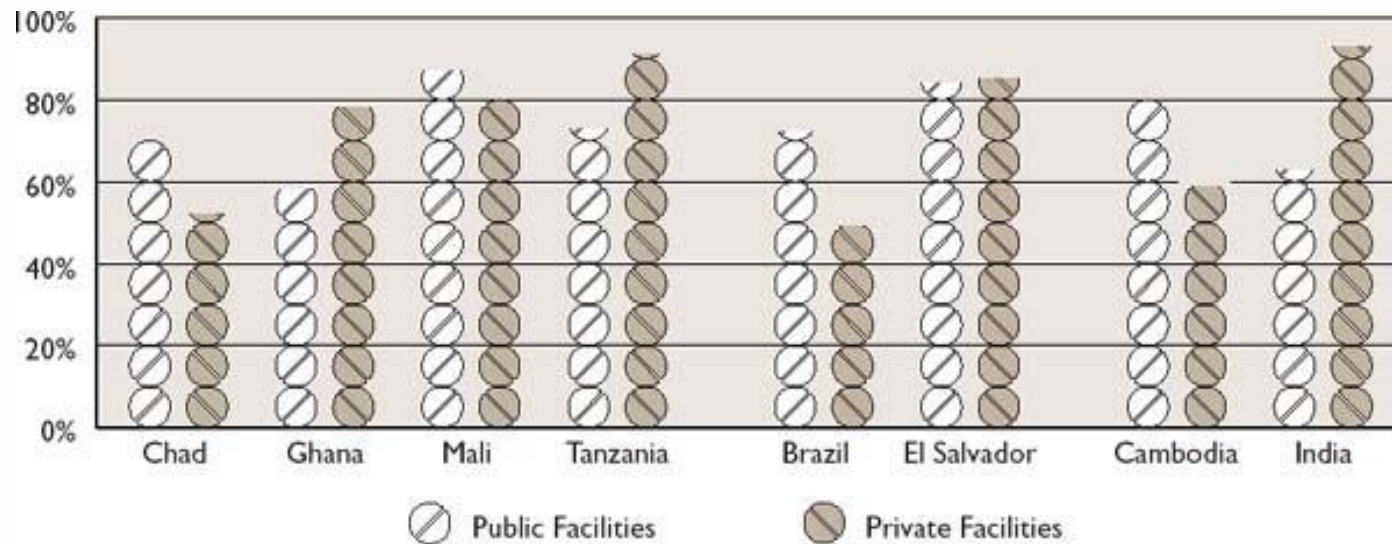
Comparison of household income to percentage of medicines obtained.

Conclusion: In countries with income <\$2/day, more patients go without some or all of their medicines compared to those with income >\$10/day

More Reasons For The List

- Lack of access to essential medicines
- Irrational use of available medicines
- Poor drug quality of available medicines

Limited Medication Availability in the Developing World



Percentage of essential medicines available for use in specified countries in public and private healthcare facilities. Medicines are not readily available for use irrespective of patient ability to purchase

Benefits

- Evidence-based rationale for the appropriate use of medicines
- Cost justification for purchasing decisions
- Allows for individualization to a country's public health needs

How the List is Used: Country-Specific Formulary

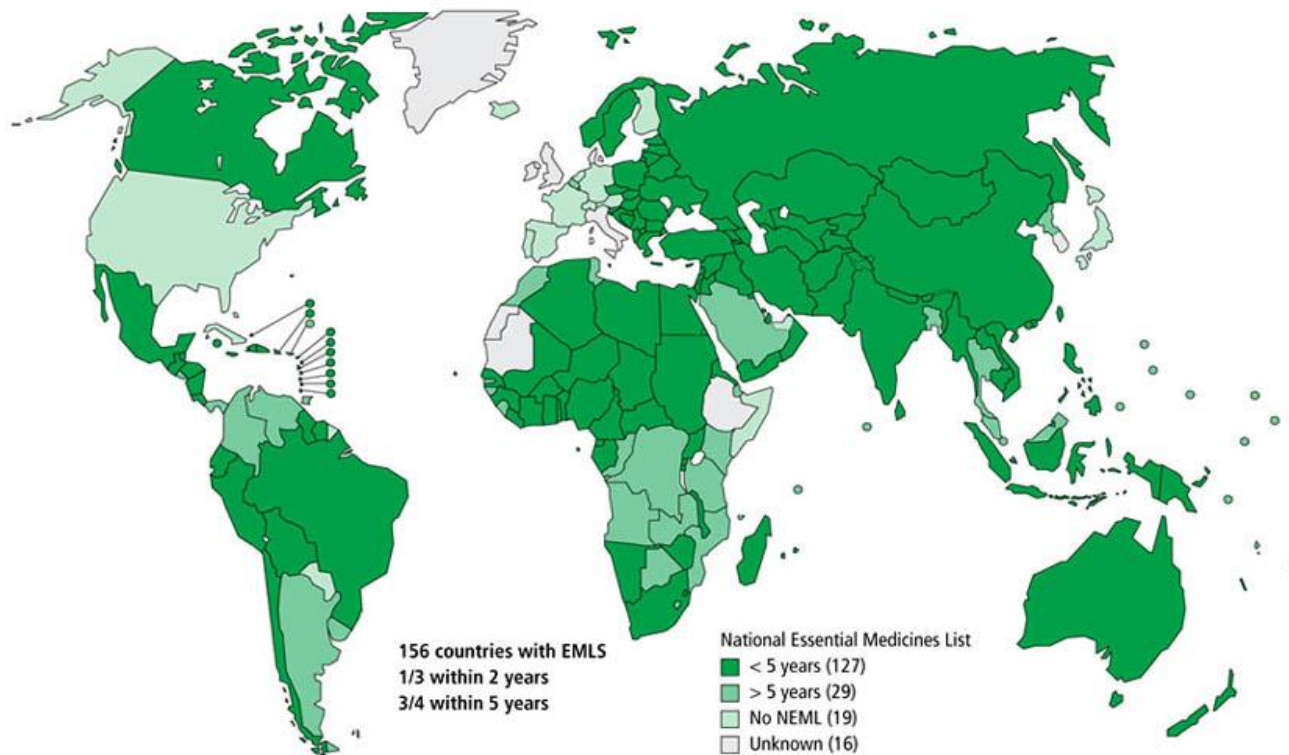
- Can be implemented on a Country, Provincial or Institutional Level
- Customizable
 - To clinical guidelines for health care practice
 - To region-specific public health issues
 - To least costly or most accessible therapeutic equivalent

Country-Specific (continued)

- In 2008
 - 156 of 193 WHO member states have official Essential Medicines Lists
 - 127 of 156 have updated lists in the past 5-10 years
 - Some have State and/or Provincial lists

http://www.who.int/topics/essential_medicines/en/

Countries with Essential Medicines Lists, 2002



How the List is Used: International Governmental Organizations

- United Nations Children's Fund (UNICEF)
- United Nations High Commission for Refugees (UNHCR)
- Guides:
 - Procurement
 - Reimbursement
 - Donations

How the List is Used: Non-Governmental Organizations (NGOs)

- International Federation of the Red Cross and Red Crescent Societies
- Médecins Sans Frontières (MSF)/ Doctors without Borders)
- Oxfam
- These groups' medicines policies are based on the Essential Medicines List concept

How the List is Used: Special Indications

- UN List of Emergency Relief Items
- Essential Medicines for Reproductive Health
- Children's Essential Medicines
- Interagency Emergency Health Kit

These lists have been instituted to supplement the full essential medicines list for specific indications. There is now a full children's essential medicines list that specifically incorporates pediatric dosage forms (e.g. suspensions, chewable tablets, disintegrating tablets). This list was first published in 2007 and is separate from the essential medicines list. The Emergency Kits are designed to provide medicines that would be effective and needed in any form of emergency (e.g. war, natural disaster, humanitarian crisis). MSF/Doctors without Borders also uses this concept in its emergency kits.

Practical Applications Of The List

- Essential Medicines List is implemented at the governmental level, but there are barriers
- Barriers
 - Infrastructure inadequacies (warehousing, distribution system, cold chain maintenance)
 - Social Inequalities/Poverty
 - Regulatory authorities, constraints
 - Intellectual Property Rights (patent protection)
 - Opposition of medical and pharmaceutical associations

Barriers: Infrastructure

A Tractor Trailer truck
Driving along Highway 1
In Niger, West Africa



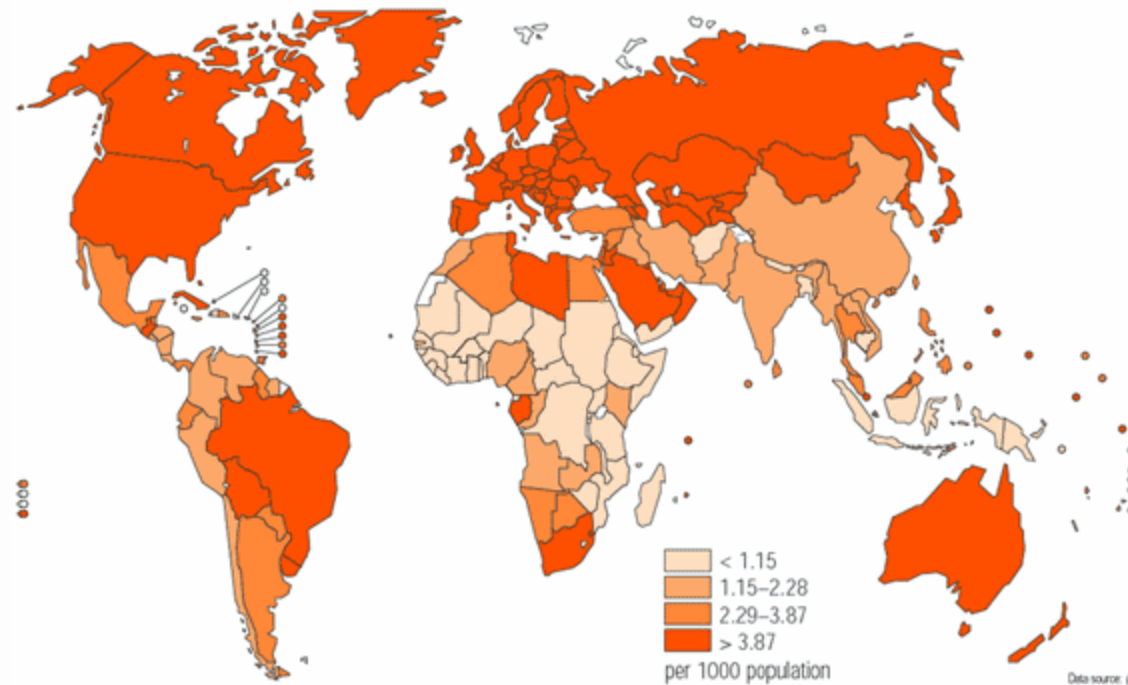
Barriers: Infrastructure

- Distribution of medicines to clinics, especially rural areas
 - Lack of roadways, adequate transportation vehicles, cold-chain
- Inadequate number and training of healthcare workers
- Limited or no access to clean water or sanitation facilities

The world health report 2006 – Working together for health. Geneva, WHO

These infrastructure barriers have become a recurring theme when discussing healthcare in the developing world and are closely intertwined with poverty both at the national and individual level. A thorough discussion of these factors is outside of the scope of this learning module, but should be understood as significant barriers to implementing the essential medicines concept.

World Distribution of Health Care Workers



Health care workers include people who provide health services, management, and support workers (e.g. cooks, driver, cleaners etc.)

The world health report 2006 – Working together for health. Geneva, WHO

Barriers: Social Inequalities and Poverty

- Inability to afford medicines, both individuals and nations
- Inadequate amounts of clean water or sanitation facilities
- Gender inequality
- Class discrimination
- Access to the healthcare system

Barriers: Regulatory

- Ability of a nation to regulate medicines including:
 - Good Manufacturing Practices (GMP)
 - Review of clinical trial data for safety, efficacy \pm cost-effectiveness
- Or, ability of nation to produce medicines:
 - Manufacturing infrastructure, GMP
 - Obtain, interpret safety and efficacy data

The regulation of medicines by the government ensures the safety and efficacy of drug products. This regulation requires significant investment by the government to review clinical trial data, ensure appropriate manufacturing practices and maintain the safety of the drug supply. The human capital required to accomplish these task is a barrier in many developing countries with relatively small budgets.

Barriers: Intellectual Property Rights

- World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS)
 - Requires all countries to respect current patents and establish ways to protect those patents, especially for brand name pharmaceuticals
 - All medicine purchasers have to pay the price negotiated with the patent holder for the branded medicine, no generics can be made or purchased
 - But, the WTO agreed to a “Public Health Emergency Clause”...

Agreement on Trade-Related Aspects of Intellectual Property Rights,
Geneva, World Trade Organization 1994

TRIPS (continued)

- In the event of a public health crisis, countries may issue “compulsory licenses” for medicines
- Allows medicines to be produced or imported without regard to patent law
- However.....
 - What constitutes a “public health crisis”?
 - In a country with infrastructure problems, how can they produce medicines?
 - If patents are respected worldwide, where can a country find generic medicines?

A full review of international intellectual property rights regulation is outside of the scope of this learning module. Please see the module dedicated to this topic on the GHEC website. A basic overview follows.

1. TRIPS- Multilateral (e.g. between multiple countries, in this case all WTO countries) trade agreement that extends patent protection to intellectual property including pharmaceuticals. Established time frame for all countries to be in compliance with the regulations. Contained a public health crisis clause that would allow a country to issue a compulsory license for a pharmaceutical; effectively allowing a patented medicine to be produced or imported as a generic with a small fee paid to the patent holder. Only allowed if the country issuing the compulsory license is unable to reach an agreement with the patent holder.
2. Doha Declaration- Allowed for countries to determine their own public health crisis. Reinforced the legality of issuing compulsory licenses.
3. TRIPS-PLUS- Bilateral (e.g. between two countries, usually the United States and a developing country) trade agreement that removes the public health crisis clause.

Compulsory Licenses Explained, Sort of...The Doha Declaration

- The Doha Declaration on Primary Health Care (2001) reiterated the concept of access to essential medicines
- Determines that “public health crisis” should be interpreted based on each country’s needs
- Compulsory licenses can be issued for any medicine that would satisfy those needs
- Problem presumably “solved”...

Doha Ministerial Declaration, Geneva World Trade Organization 2001

Consequences of Doha Declaration

- Most countries can still not afford to produce their own medicines, but generics can now be imported (e.g., from India, Brazil)
- Countries that have issued compulsory licenses have faced sanctions from the developed world (e.g., South Africa issued licenses for some anti-retrovirals to treat HIV/AIDS in the 1990s and faced sanctions from the United States)

Consequences (continued)

- Bilateral Trade Agreements (between two countries only)
- Known as TRIPS Plus, agreements are usually between the U.S. and a developing country
- Agreements specifically exclude the public health crisis and compulsory licenses provision
- Overrides the original WTO TRIPS agreement

Notes on Consequences.

Bilateral trade agreements are usually between a developed country (e.g. the United States, European Union countries etc.) and a developing country. These agreements are generally stricter than the TRIPS agreement, especially in the ability of developing countries to issue compulsory licenses. For example, the U.S. may enter into an agreement with a developing country that offers that country a more favorable trade relationship. In return, the developing country agrees to more stringent patent protection on goods from the U.S. The developing country may no longer be able to issue a compulsory license on a medication from a U.S. pharmaceutical manufacturer. But, these bilateral agreements, being only between two countries, do not affect the developing countries ability to issue a compulsory license on a medicine produced by a E.U. pharmaceutical company, (assuming there are no other bilateral trade agreements in effect) TRIPS would still apply in that relationship.

Opposition from Medical and Pharmaceutical Associations

- Some policies focused on rationale use of medicines through clinical guidelines, believed to limit clinician judgment or choice (opposed by medical associations)
- Some focused on promoting country specific pharmaceutical companies, limiting access to other medicines (opposed by pharmaceutical companies)
- Some limited to only generic medicines (opposed by both medical and pharmaceutical associations)

Take Home Points...

- Essential Medicines are an indispensable component of a healthcare system
- WHO provides an Essential Medicines List that may be used as a framework for developing a national, regional or NGO formulary
- The WHO list is updated biannually by expert committee and takes into account new medicines, efficacy, safety and cost-effectiveness

Take Home Points (continued)

- The Essential Medicines concept has been widely adopted in WHO member countries, though widespread access to these medicines is still limited
- Numerous barriers to implementing the list still exist, specifically infrastructure development problems and international agreements on intellectual property rights that limit medicine availability
- Many of the barriers in implementing essential medicines are similar if not identical to barriers facing widespread health care system development

- **Context:** Thailand is experiencing an HIV/AIDS epidemic. There are a limited number of anti-retroviral treatment options available. One of the mainstays of treatment at this time is a combination protease inhibitor known as Kaletra ® (lopinavir/ritonavir) produced by Abbott Laboratories. At the time there is no generic available.
- **Problem:** The cost of treatment with Kaletra is more than the Thai government is able to afford. Abbott Laboratories is unable to negotiate a compromise on price with the government.
- **Solution:** The Thai government exercised its legal right to issue a compulsory license to import and produce a version of Kaletra to treat a public health crisis. The government complied with all aspects of TRIPS and the Doha Declaration.
- **Effects:** Abbott Laboratories withdrew all applications for new products to be introduced in Thailand including a heat-stable version of Kaletra. Abbott also ceased shipping all of its pharmaceuticals to Thailand. Thailand was placed on the United States Priority Watch List; a list of nations that have “violated” international treaties on intellectual property. Abbott eventually was able to negotiate with the government on a price comparable with available generics. Thailand has not rescinded the compulsory license.
- **Analysis:** Thailand was within its legal rights to issue a compulsory license for Kaletra after negotiations with Abbott failed to render a compromise. The government also agreed to pay Abbott 0.5% of the proceeds from the license. The repercussions, however, were quick and severe. Thailand lost access to many more medicines than it gained. Thailand also remains on the U.S. Priority Watch List, hindering future trade negotiations with the developed world.

Quiz

- Now we invite you to take the module quiz and test your recent learning.
- This module quiz includes 5 multiple choice questions
- Note your answers on a piece a paper and then check them against the correct responses
- After completing your quiz, come back for the general references of this module presentation.

1. Which of the following is NOT part of the rationale for the creation of the Essential Medicines List?

- A Medicines are one of the largest expenditures of healthcare dollars in developing countries
- B Essential medicines are a necessity to the provision of primary health care
- C Essential medicines help to protect intellectual property rights
- D Essential medicines correspond with priority health needs

2. A novel antifungal was recently approved in the European Union. It is only available as an intravenous formulation and is minimally more effective than current antifungals. Where would this medicine be added on the Essential Medicines List?

- A The Core List
- B The Complementary List
- C A Therapeutic Equivalent
- D It would not be added to the list at this time

3. The concept of essential medicines has been instituted in most countries throughout the world. Which of the following is NOT a direct benefit of the essential medicines list?

- A Provided a clinical guideline for the appropriate use of medicines
- B Increased availability of medicines in healthcare systems
- C Focused on region specific health public health issues Incorrect
- D Guided use to least costly or most widely available medicines

4. Achieving full implementation of the essential medicines list has been derailed by numerous barriers. Which of the following barriers is considered mostly a developed world impediment to the goals of the list?

- A Intellectual property rights and patent law
- B Poverty at either a personal or country level
- C Inadequate numbers of healthcare workers in the developing world
- D Distribution and cold-chain supply problems

5. The TRIPS agreement by the WTO is a major barrier to access medicines in developing countries. Which of the following best describes the current state of thinking regarding TRIPS by most developing countries?
- A TRIPS agreements are legal documents that must be complied with fully; compulsory licenses are effectively illegal
 - B The multilateral trade agreements do not fully protect intellectual property and must be supplemented by more stringent bilateral agreements
 - C Compulsory licenses may only be issued during significant public health crises and will be limited to the duration of the crisis (e.g. cholera outbreaks)
 - D Compulsory licenses can and should be issued to treat public health crises as determined by the developing country but only after negotiations with the patent holder have failed to produce an effective solution

**And now for the answers
to the questions**

1. Which of the following is NOT part of the rationale for the creation of the Essential Medicines List?

- A Medicines are one of the largest expenditures of healthcare dollars in developing countries -- Incorrect. -- Medicines account for up to 60% of healthcare dollars spent in developing countries
- B Essential medicines are a necessity to the provision of primary health care
Incorrect. -- Essential medicines are specified in the Alma-Ata Declaration on Health
- C Essential medicines help to protect intellectual property rights -- **Correct.** -
- Intellectual property rights are considered a barrier to the implementation of essential medicines
- D Essential medicines correspond with priority health needs -- Incorrect.

2. A novel antifungal was recently approved in the European Union. It is only available as an intravenous formulation and is minimally more effective than current antifungals. Where would this medicine be added on the Essential Medicines List?

A The Core List -- Incorrect. -- While this medicine may treat a priority condition, it requires special administration (IV) and is only minimally more effective than current treatments

B The Complementary List -- Incorrect. -- This may be an appropriate category for the medicine, however without cost-effectiveness or cost-comparison information, the medicine will not be added or reviewed.

C A Therapeutic Equivalent -- Incorrect. -- This is a novel new medicine and most likely will not have a therapeutic equivalent

D It would not be added to the list at this time -- **Correct** . -- Without cost information, this medicine will not be reviewed or added to the essential medicines list

3. The concept of essential medicines has been instituted in most countries throughout the world. Which of the following is NOT a direct benefit of the essential medicines list?

- A Provided a clinical guideline for the appropriate use of medicines
- B Increased availability of medicines in healthcare systems -- **Correct.** --
This is the overall intention of the list, but the list does not directly increase availability of medicines
- C Focused on region specific health public health issues Incorrect
- D Guided use to least costly or most widely available medicines

4. Achieving full implementation of the essential medicines list has been derailed by numerous barriers. Which of the following barriers is considered mostly a developed world impediment to the goals of the list?

A Intellectual property rights and patent law -- **Correct.** -- These laws were propagated by the developed world and pharmaceutical companies to inhibit local production of medicines in the developing world

B Poverty at either a personal or country level -- Incorrect. -- While the origins of developing world poverty may be attributable to colonization or imperialism, it is generally not considered that the developed world is imposing poverty on developing countries

C Inadequate numbers of healthcare workers in the developing world -- Incorrect. -- Though healthcare workers trained in the developing world are more likely to immigrate to developed countries, this is not due to any developed countries policies. In many developed countries, there are policies regarding training healthcare workers from the developing world, but not allowing them to receive visas or immigration status after completing their training

D Distribution and cold-chain supply problems -- Incorrect.

5. The TRIPS agreement by the WTO is a major barrier to access medicines in developing countries. Which of the following best describes the current state of thinking regarding TRIPS by most developing countries?

A TRIPS agreements are legal documents that must be complied with fully; compulsory licenses are effectively illegal -- Incorrect. -- Most countries recognize the validity of compulsory licenses for public health

B The multilateral trade agreements do not fully protect intellectual property and must be supplemented by more stringent bilateral agreements -- Incorrect. -- Developed countries, particularly the United States, have taken this stand point

C Compulsory licenses may only be issued during significant public health crises and will be limited to the duration of the crisis (e.g. cholera outbreaks -- Incorrect. -- This is the assumed original intent of the compulsory license clause. These licenses would be issued for a limited duration for diseases that could be effectively cured in the short term; it was not intended for chronic diseases (e.g. HIV/AIDS)

D Compulsory licenses can and should be issued to treat public health crises as determined by the developing country but only after negotiations with the patent holder have failed to produce an effective solution -- **Correct.** -- Most developing countries have taken this approach to maintain current trade relations with the developed world while managing the welfare of their own population

General References

Papers:

- Sridhar D, Improving Access to Essential Medicines: How Health Concerns can be Prioritised in the Global Governance System. Public Health Ethics. 2008,1(2):83-88
- Koivusalo M, Mackintosh M. Global Public Action in Health and Pharmaceutical Policies: Politics and Policy Priorities. The Open University February 2009

Web Links:

- WHO Essential Medicines http://www.who.int/topics/essential_medicines/en/
Gateway to the WHO program on essential medicines including the Expert Committee, Published Essential Medicines Lists and statistics.
- WHO <http://www.who.int>
Entry to the WHO website. Provides access to published reports, statistics and WHO programs.
- WTO <http://www.wto.org>
Entry to the World Trade Organization website. Provides access to published reports, statistics and WTO trade agreements.

Credits

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Supplementary Notes

Slide 5: Defining Essential Medicines

The full definition of essential medicines is given below. The main point of this definition is to reinforce that the list is not a permanent list of must have medicines but rather a guide. Each country must determine its own list based on the current and future public health needs, and availability of medicines.

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Slide 11: Therapeutic Equivalence

Therapeutic equivalence indicates that medicines have similar clinical efficacy, though there may be some benefits of one medicine over another based on dosing frequency or side effect profile. In the U.S. the most common example of drugs with therapeutic equivalence are the HMG-CoA Reductase Inhibitors or “Statins” (e.g. Rosuvastatin, atorvastatin, simvastatin, lovastatin, pravastatin)

to Slide 11

Slide 26: How the List is Used: Special Indications

These lists have been instituted to supplement the full essential medicines list for specific indications.

There is now a full children's essential medicines list that specifically incorporates pediatric dosage forms (e.g. suspensions, chewable tablets, disintegrating tablets). This list was first published in 2007 and is separate from the essential medicines list.

The Emergency Kits are designed to provide medicines that would be effective and needed in any form of emergency (e.g. war, natural disaster, humanitarian crisis). MSF/Doctors without Borders also uses this concept in its emergency kits.

to Slide 26

Slide 29: Barriers: Infrastructure

These infrastructure barriers have become a recurring theme when discussing healthcare in the developing world and are closely intertwined with poverty both at the national and individual level. A thorough discussion of these factors is outside of the scope of this learning module, but should be understood as significant barriers to implementing the essential medicines concept.

to Slide 29

Slide 32: Barriers: Regulatory

The regulation of medicines by the government ensures the safety and efficacy of drug products. This regulation requires significant investment by the government to review clinical trial data, ensure appropriate manufacturing practices and maintain the safety of the drug supply. The human capital required to accomplish these tasks is a barrier in many developing countries with relatively small budgets.

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Slide 33: Barriers: Intellectual Property Rights

For notes, see Teaching Modules Appendix:

<http://globalhealtheducation.org/Modules/Teaching%20Modules%20Appendix/106.aspx>.

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Note G:

Consequences

Bilateral trade agreements are usually between a developed country (e.g. the United States, European Union countries etc.) and a developing country. These agreements are generally stricter than the TRIPS agreement, especially in the ability of developing countries to issue compulsory licenses. For example, the U.S. may enter into an agreement with a developing country that offers that country a more favorable trade relationship. In return, the developing country agrees to more stringent patent protection on goods from the U.S. The developing country may no longer be able to issue a compulsory license on a medication from a U.S. pharmaceutical manufacturer. But, these bilateral agreements, being only between two countries, do not affect the developing countries ability to issue a compulsory license on a medicine produced by a E.U. pharmaceutical company, (assuming there are no other bilateral trade agreements in effect) TRIPS would still apply in that relationship.

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