Session 4:

The Drug Management Cycle: Selection

David Peters

Unit Objectives

1. Be able to apply evidence-based criteria for pharmaceutical product selection

2. Describe approaches to developing Essential Medicines Lists, Formularies, and Standard Treatment Guidelines

3. Recognize the challenges in implementing treatment guidelines and formulary systems and ways to overcome them

Session Outline

1. Introduction (case)
2. Key Definitions
3. Approaches to Implementation
4. Implementation Issues
5. Summary of Session

Why Be Selective With Drugs?

- Drugs represent a large part of the public health budget
- Funds are limited
- Large numbers of drugs are available
- Impossible to keep up-to-date with all the drugs on the market

Reasons to Support Rational Selection

- Promotes improved drug availability
- Regular drug supply can improve health outcomes
- Prescribers can become familiar with a smaller number of drugs
- Improved drug therapy can lower health care costs
- Procurement, storage, and distribution are simplified
- Buying larger quantities of fewer drugs can lower procurement costs
- Facilitates drug information and education efforts

Selection Options

- Formulary list = Essential medicines list
- Formulary manual
- Formulary system

Definition of Essential Medicines

- Are those that satisfy the priority health care needs of the population
- Are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness
- 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 cost that individuals and the community can afford

Definition of a Medicines Formulary

- **Formulary List** – Medicines approved for use in the health care system by authorized prescribers

- **Formulary Manual** – The document that describes medicines that are available for use in the hospital and clinics (provides information and indications, dosage, length of treatment, interactions, contraindications, etc.)

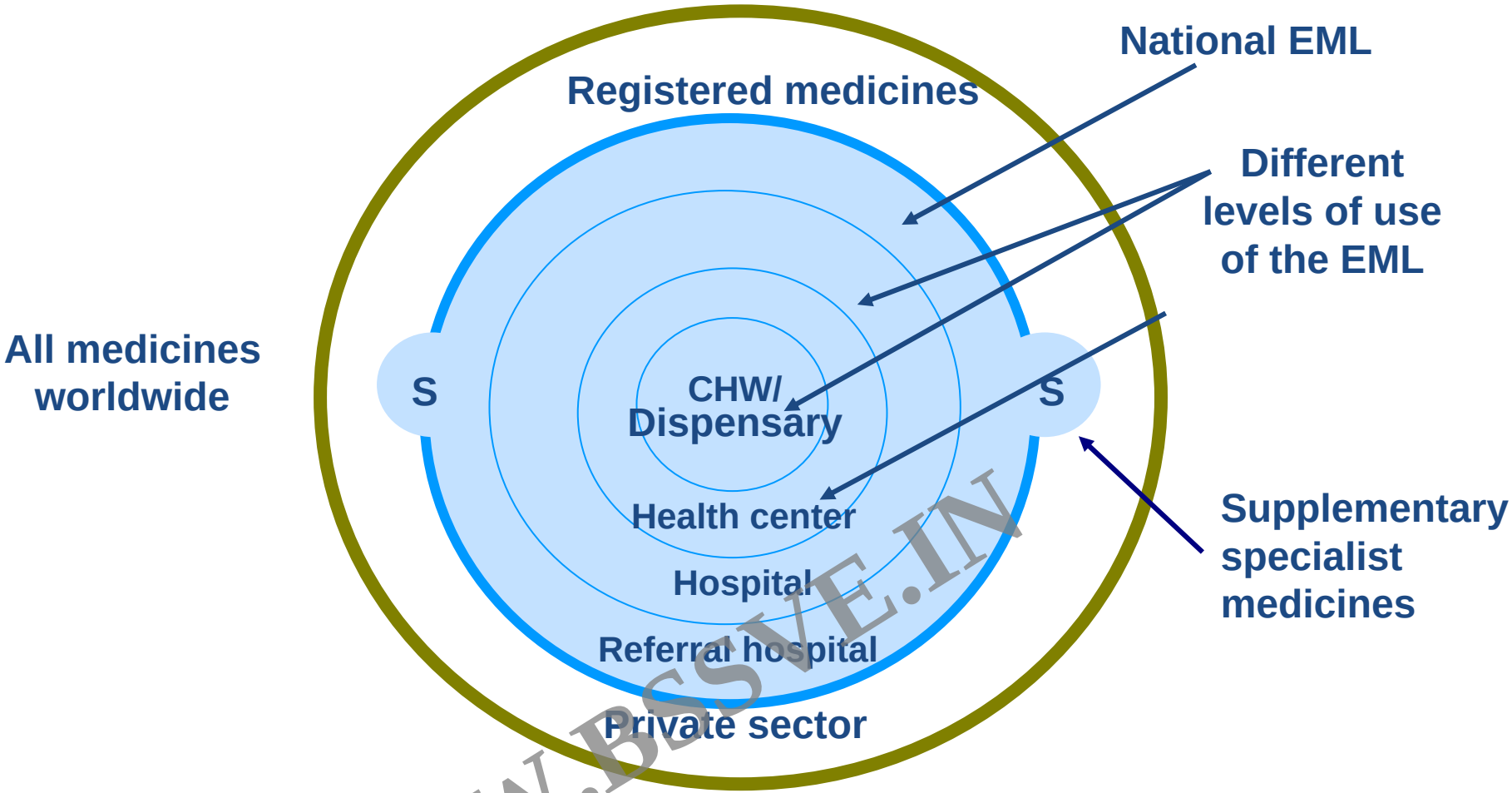
Source: MSH: *Managing Drug Supply.* 2nd ed. West Hartford, CT: Kumarian Press, 1997.

Standard Treatment Guideline

- A systematically developed statement designed to assist practitioners and patients in making decisions about appropriate treatment for specific clinical circumstances

Source: MSH: *Managing Drug Supply.* 2nd ed. West Hartford, CT: Kumarian Press, 1997.

The Essential Medicines Target



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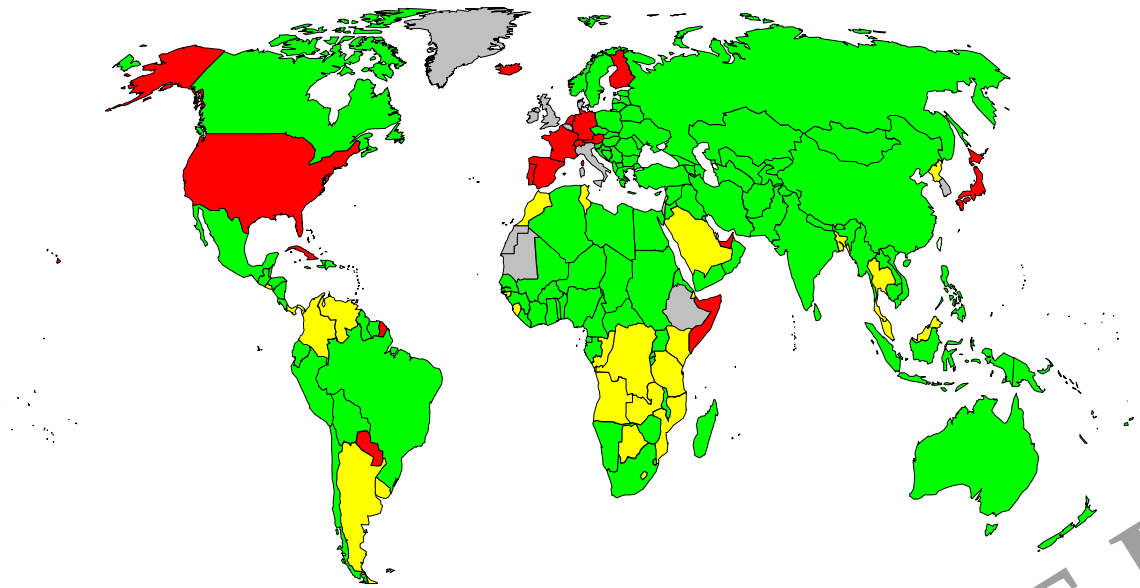
156 Countries with Essential Medicines Lists



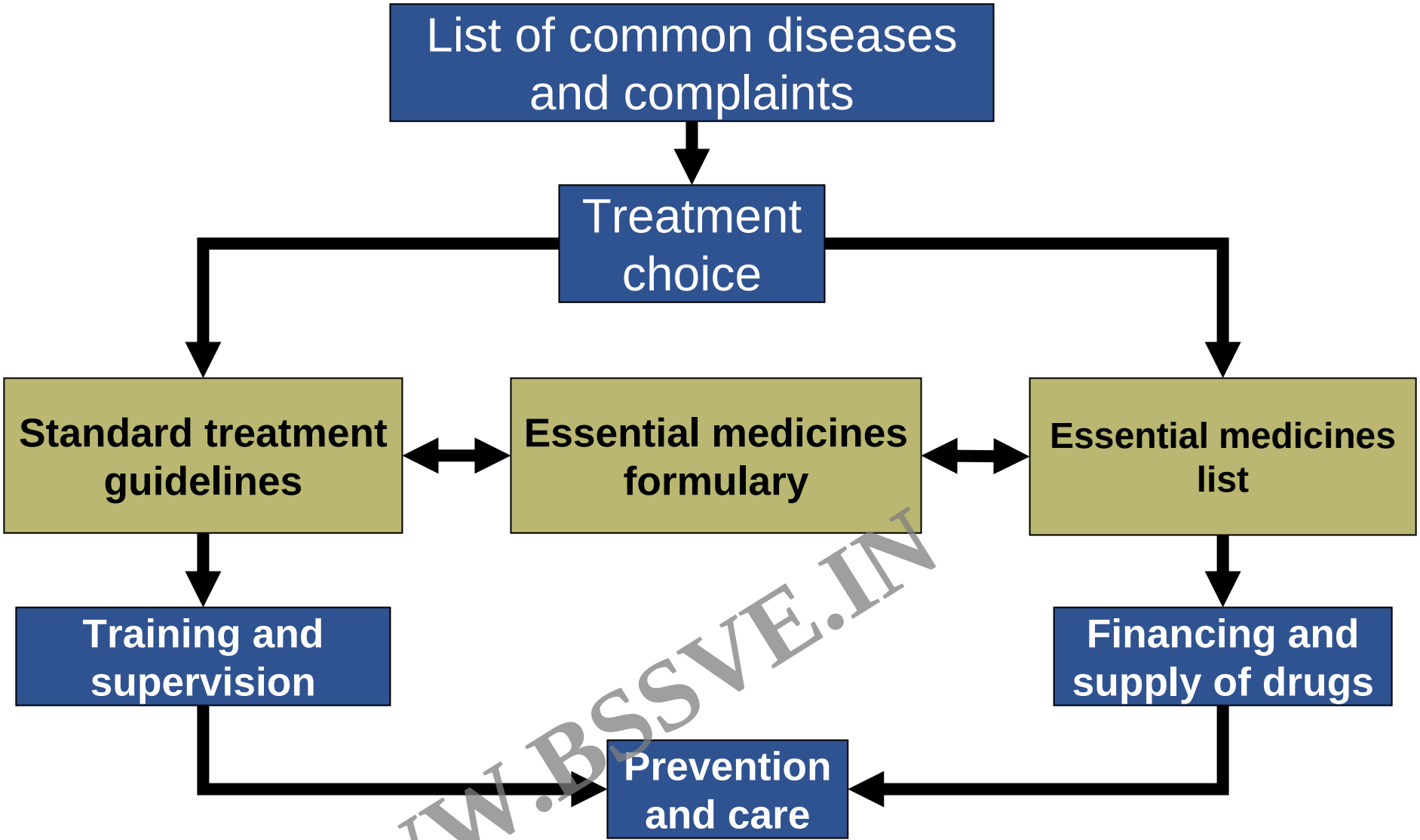
There are 156 countries with an official selective list for training, supply, reimbursement, or related health objectives. Some countries have selective state/provincial lists instead of or in addition to national lists.

Approaches to Implementation

- Build list based on most common health problems
- Start with existing list of drugs
- Tips:

  selection by committee

  coordinate selection and procurement activities



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Drug Selection Criteria

- *Need* based on prevalent disease patterns
- *Personnel* capable of using the drugs
- *Financial resources* available
- *Safety and efficacy* demonstrated and documented
- *Quality*, bioavailability, and stability

Drug Selection Criteria, cont.

- *Therapeutic equivalence* of drugs based on efficacy, safety, quality, price, and availability
- *Total cost of treatment,* not only the unit cost of the drug
- *Proven advantage of combination products* over single compounds being used separately

Use of International Nonproprietary (Generic) Names

- **Advantages of generic products:**
  - names are more informative
  - often less expensive
  - generic prescribing facilitates substitution

- **Arguments against generic products:**
  - inferior and have bioequivalence problems
  - names are hard to remember

Therapeutic Classification Schemes

- Provide a framework for drafting list
- The formulary manual is organized according to the scheme chosen
- It is reasonable to use or adapt an existing scheme

Use of Information

- Sources of current information are often limited
- Some references commonly used by formulary committees include:

  Martindale: The Extra Pharmacopoeia

  The AMA Drug Evaluations Annual

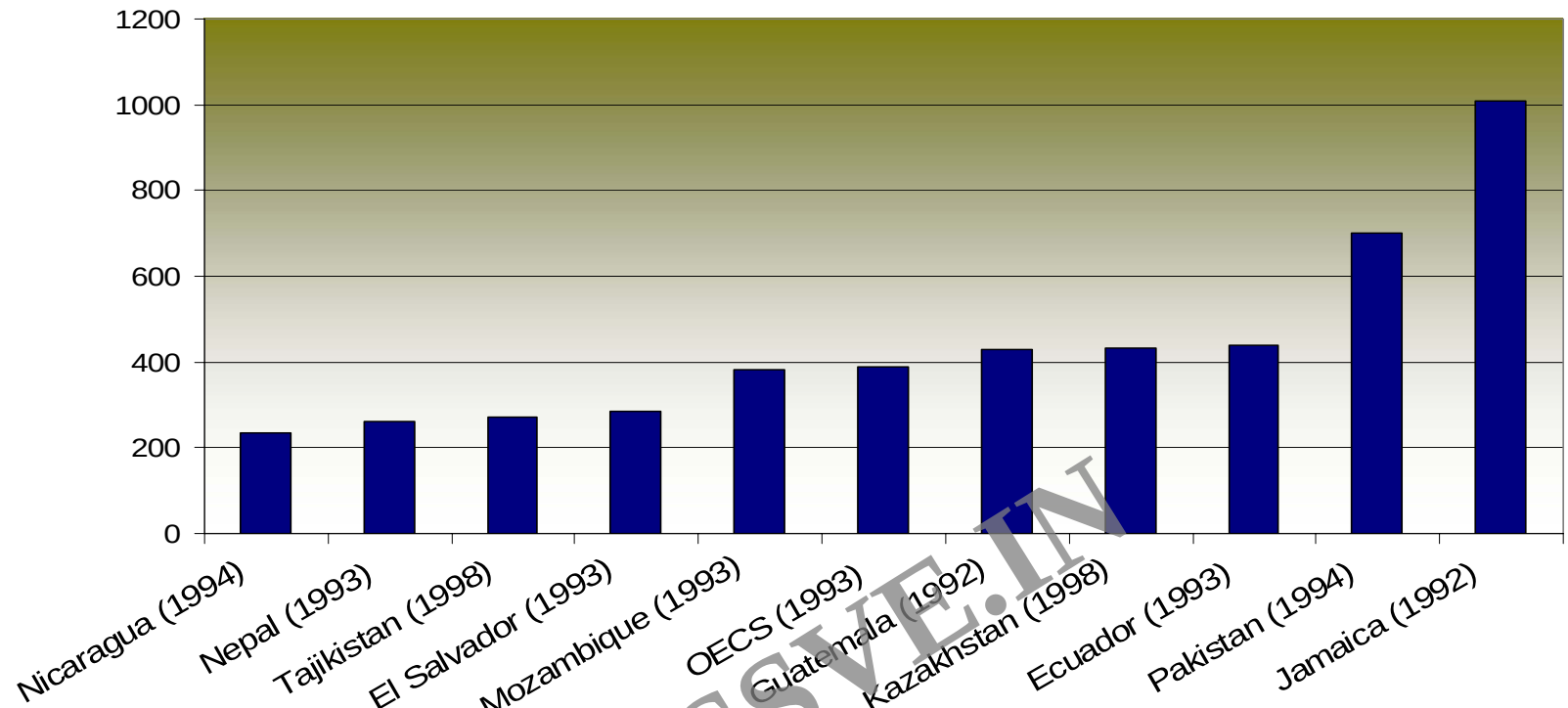
  The British National Formulary

  Medical Letter on Drugs and Therapeutics

Role of Drug and Therapeutics Committees

- Develop or adapt STGs
- Assess adherence to STGs
- Develop and implement appropriate strategies to ensure adherence

Number of Medicines on National Essential Medicines Lists



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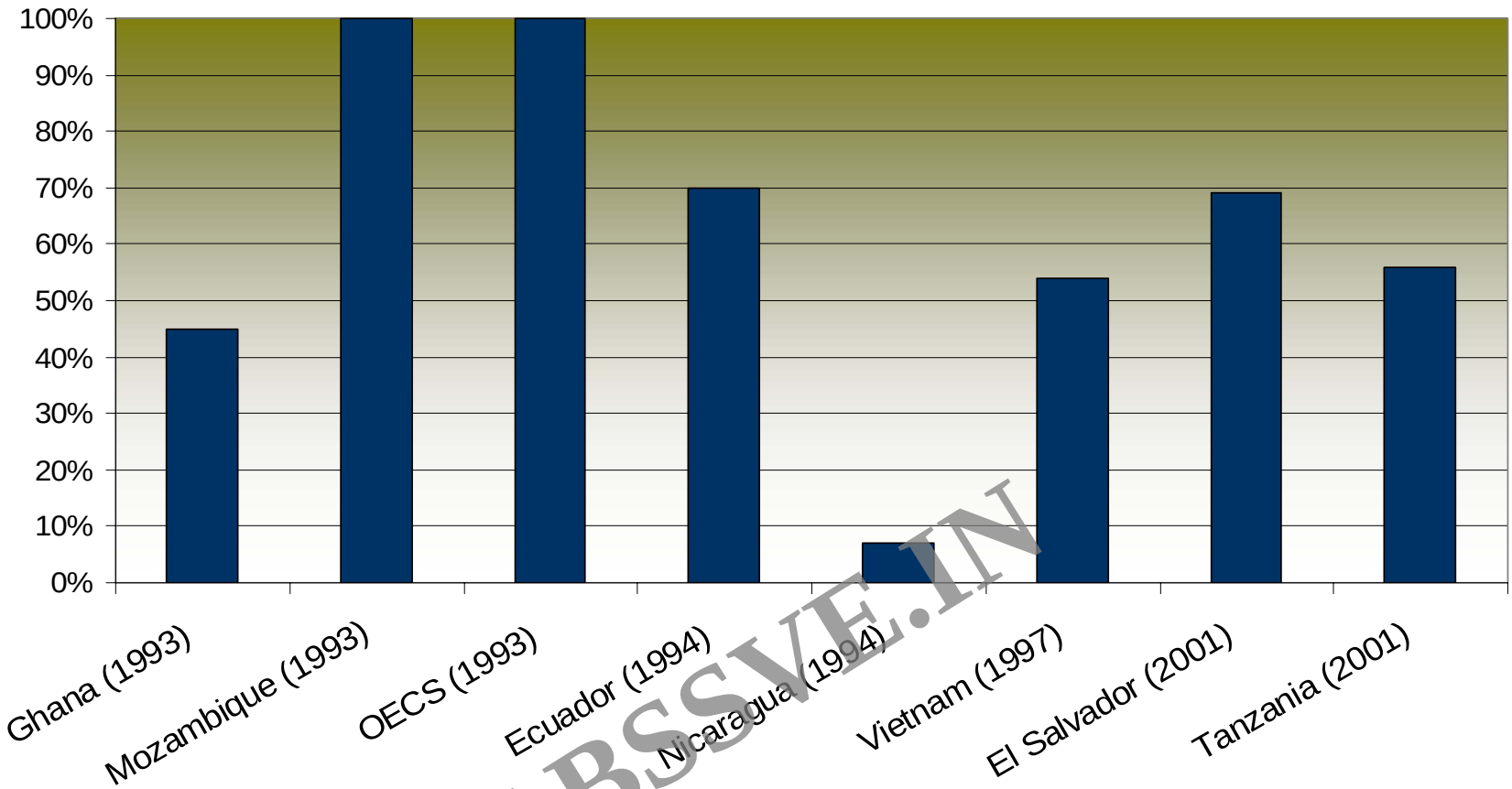
Availability of EMLs in Health Facilities



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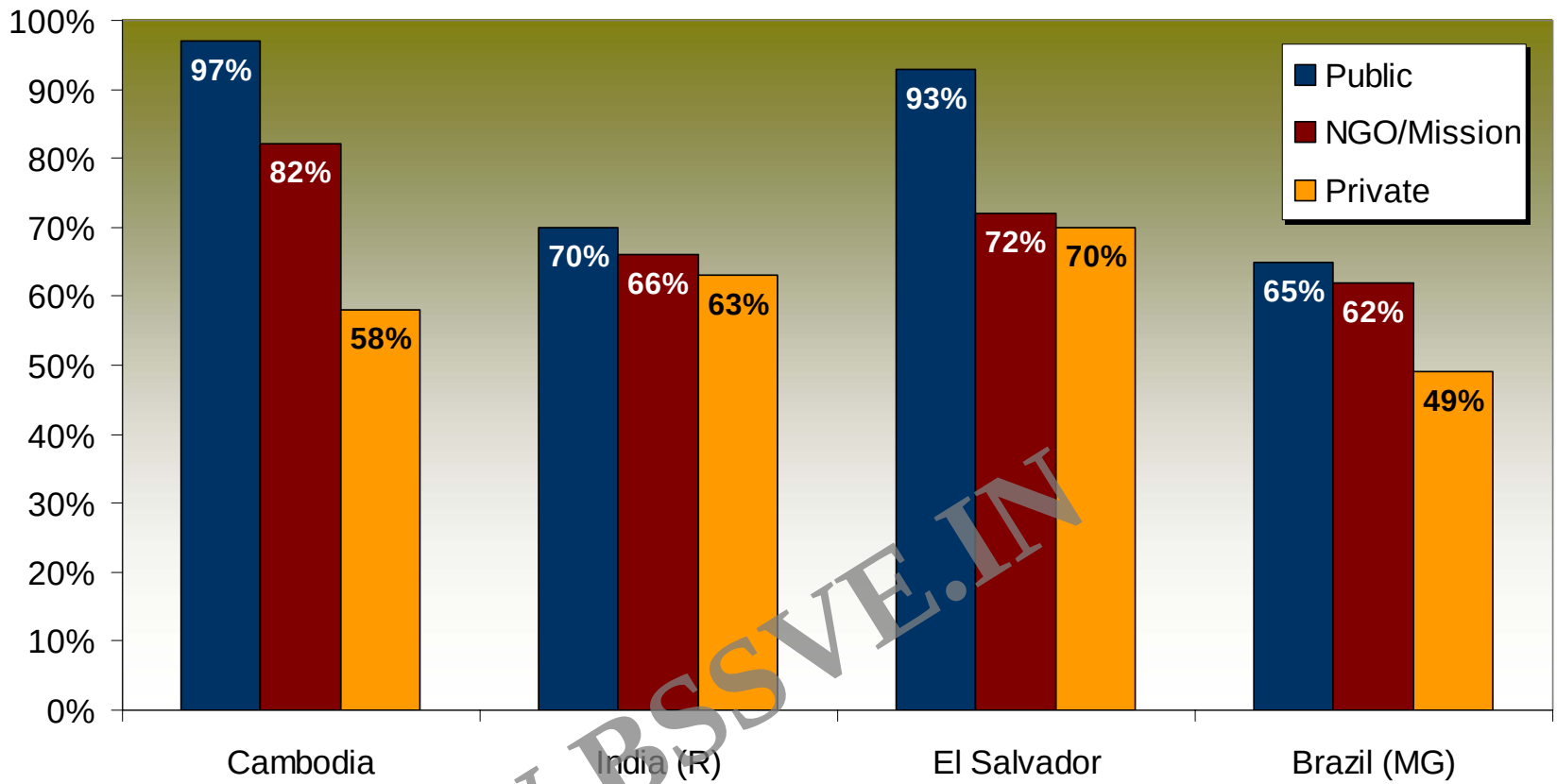
Percentage of Medicines Prescribed from EML, by Sector



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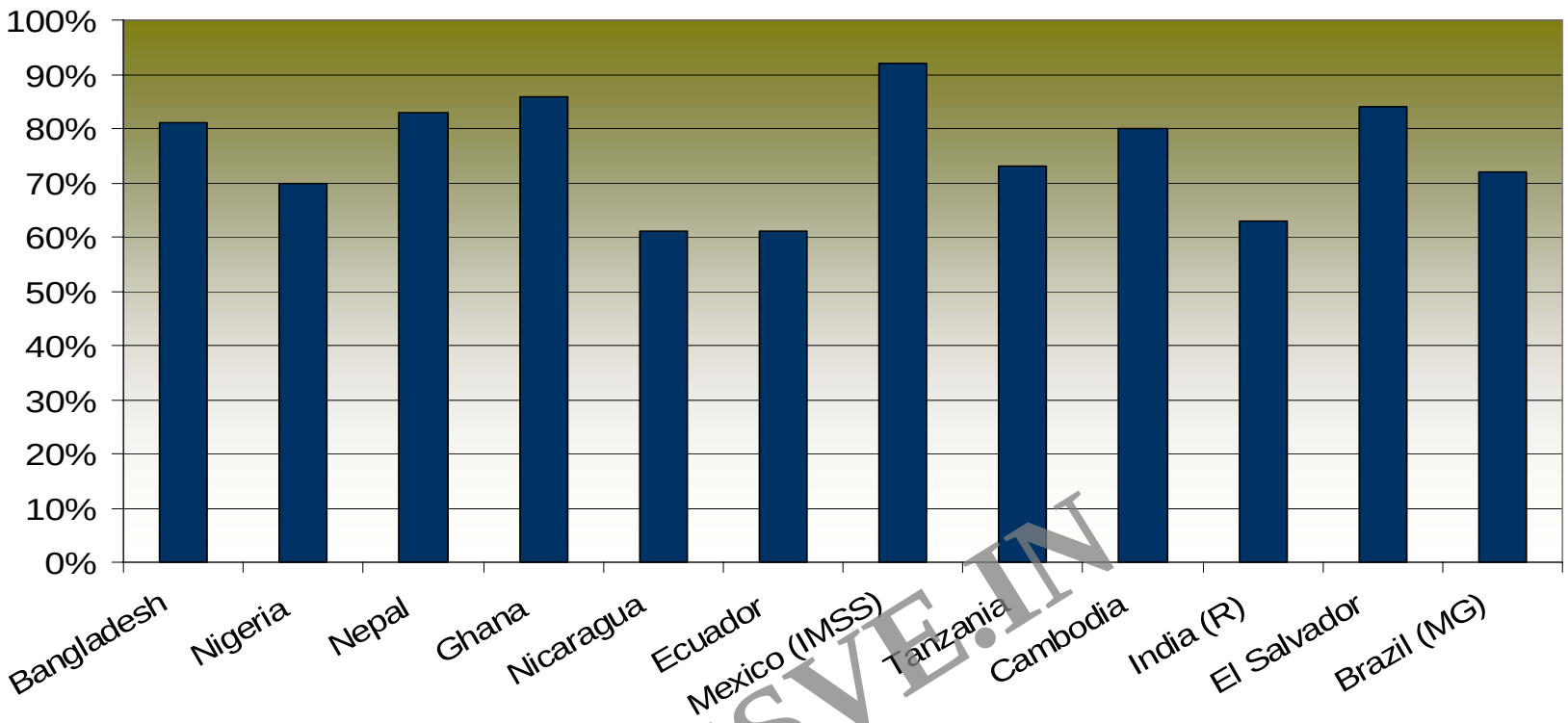
Percentage of Prescribed Medicines That Were Actually Dispensed



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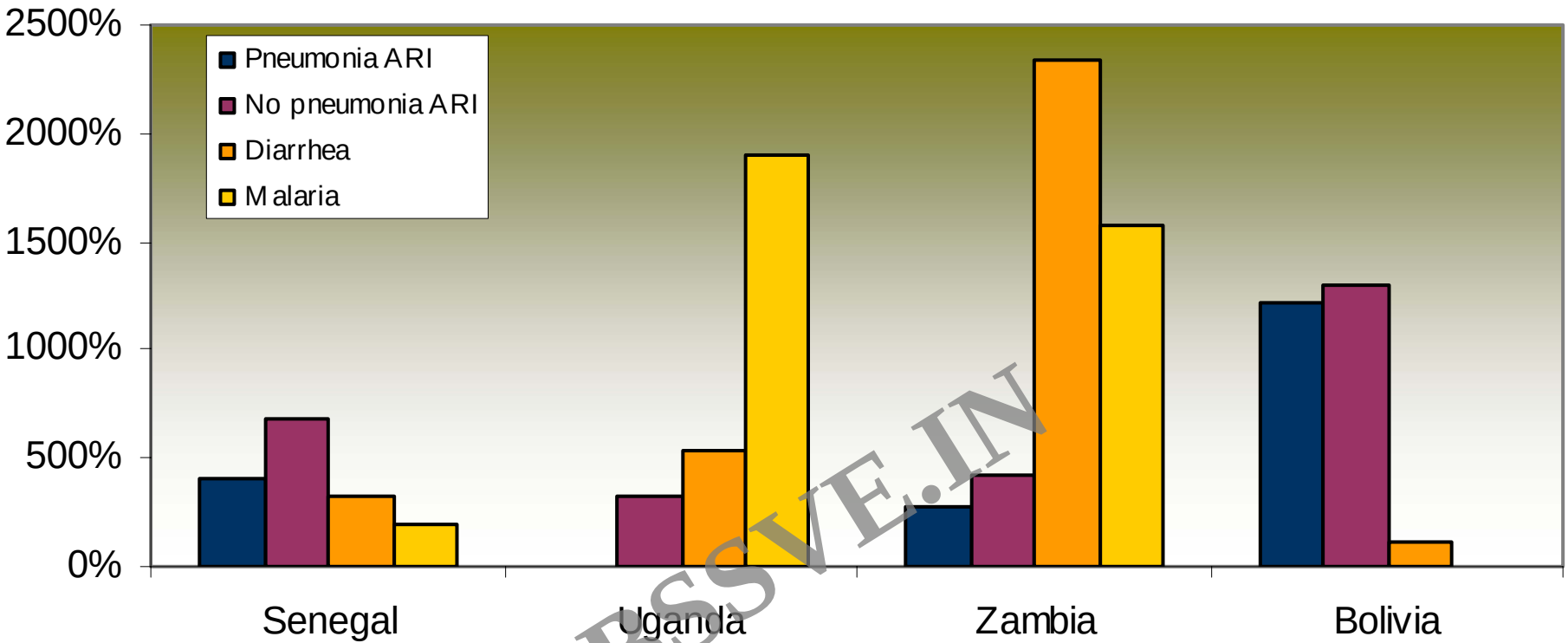
Average Cost of Medicines Prescribed as a Percentage of Cost if IMCI Treatment Guidelines Were Followed



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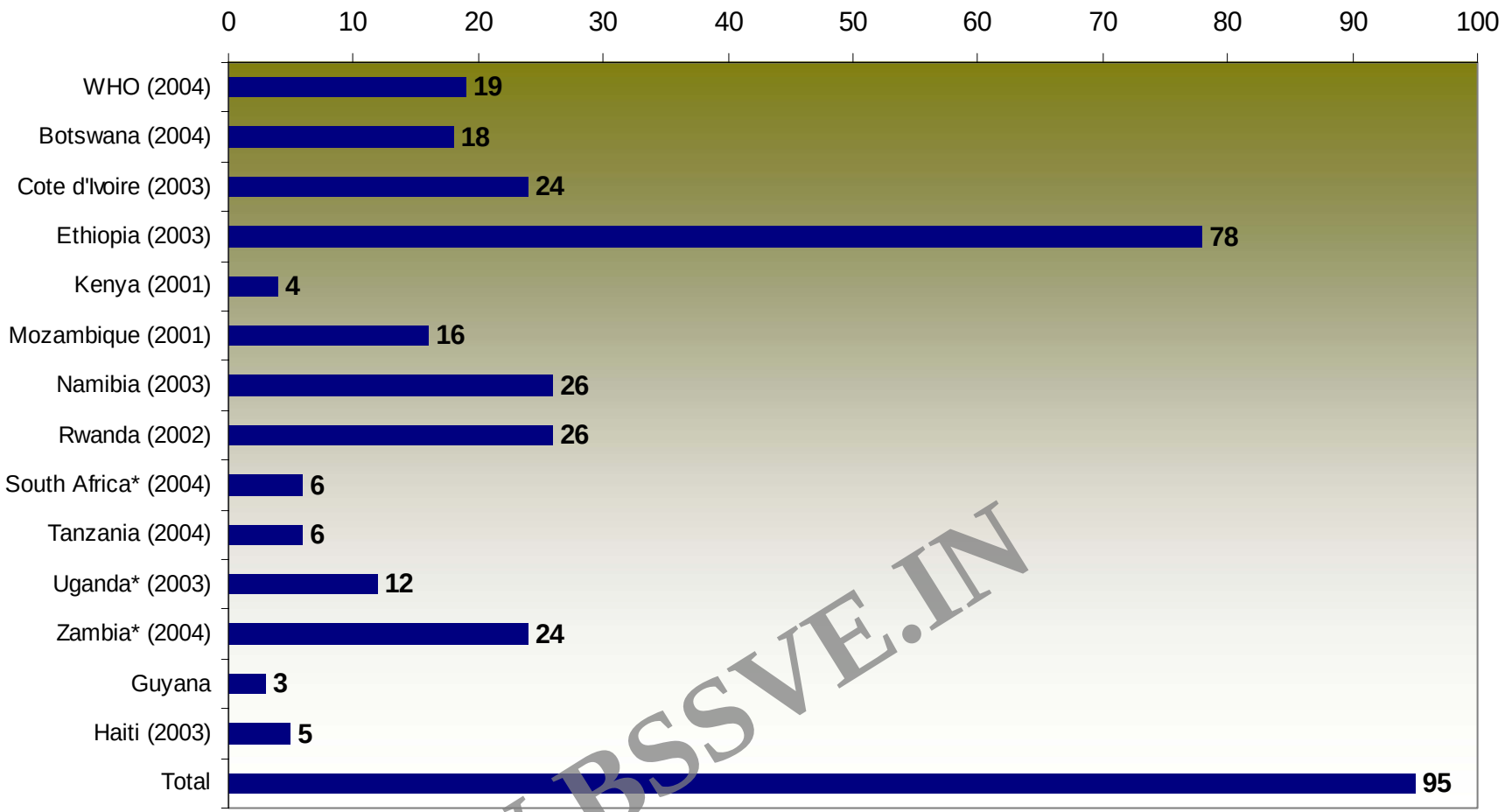
Examples of Standard Treatment Guidelines

HIV/AIDS-Related Pharmaceuticals

- Antiretrovirals (ARVs):
  - Postexposure prophylaxis
  - Prevention of mother-to-child transmission
  - Clinical AIDS
- Anti-infectives (antibacterials, antifungals, and antivirals) for prevention and treatment of opportunistic infections
- Treatment of sexually transmitted infections (STIs)
- Tuberculosis treatment
- Analgesics and palliative care pharmaceuticals
- Anticancer pharmaceuticals
- Pharmaceuticals for noninfectious and other complications:
  - Cardiac
  - Renal
  - Hepatic
  - Neuropathic
  - Dermatologic
  - Hematologic
  - Pulmonary
  - Gastrointestinal/diarrhea
  - Oral and esophageal
  - Psychiatric

Adult ART Regimens Included in STGs



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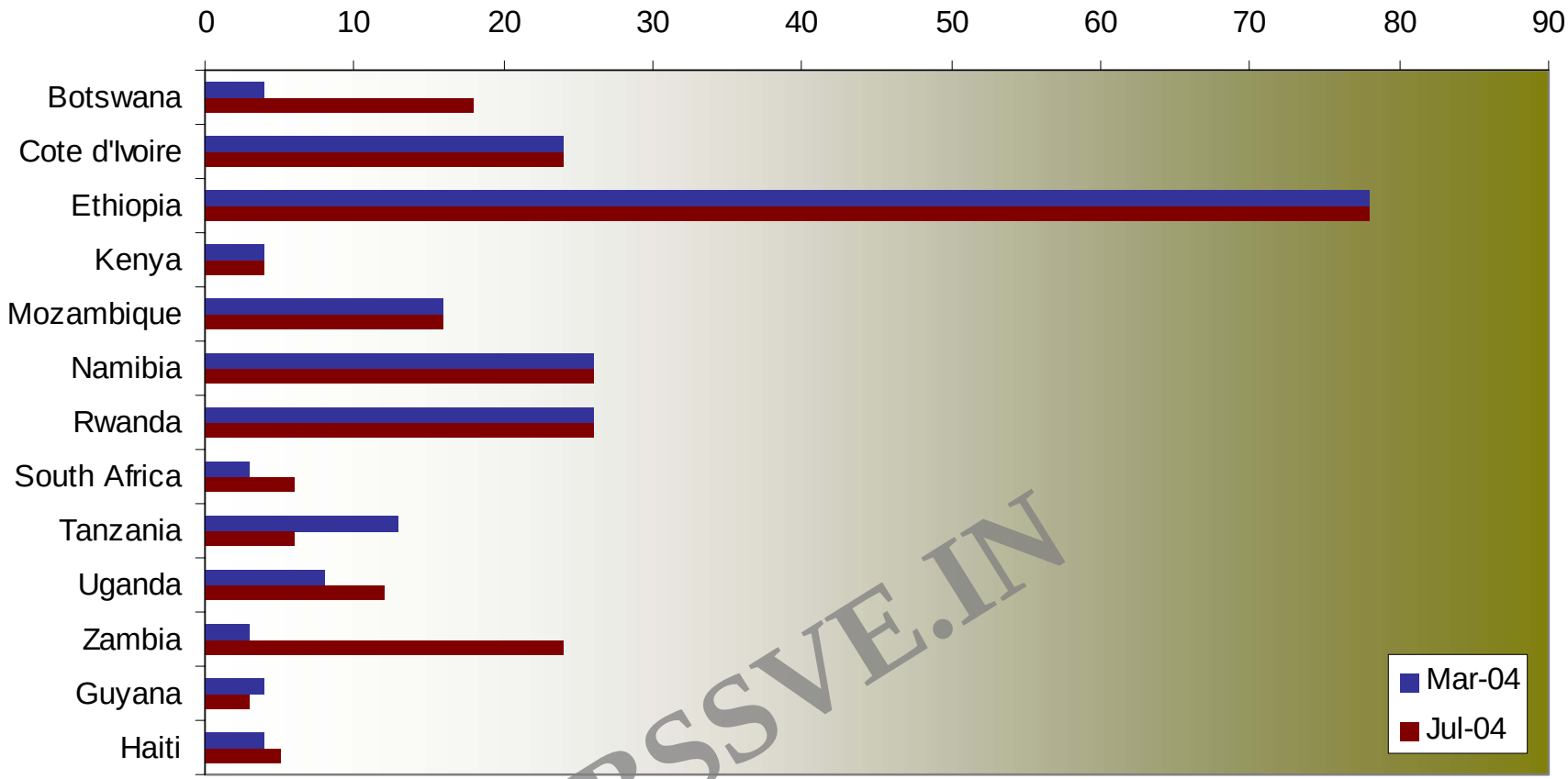
Changes in No. of Adult ART Regimen in STGs



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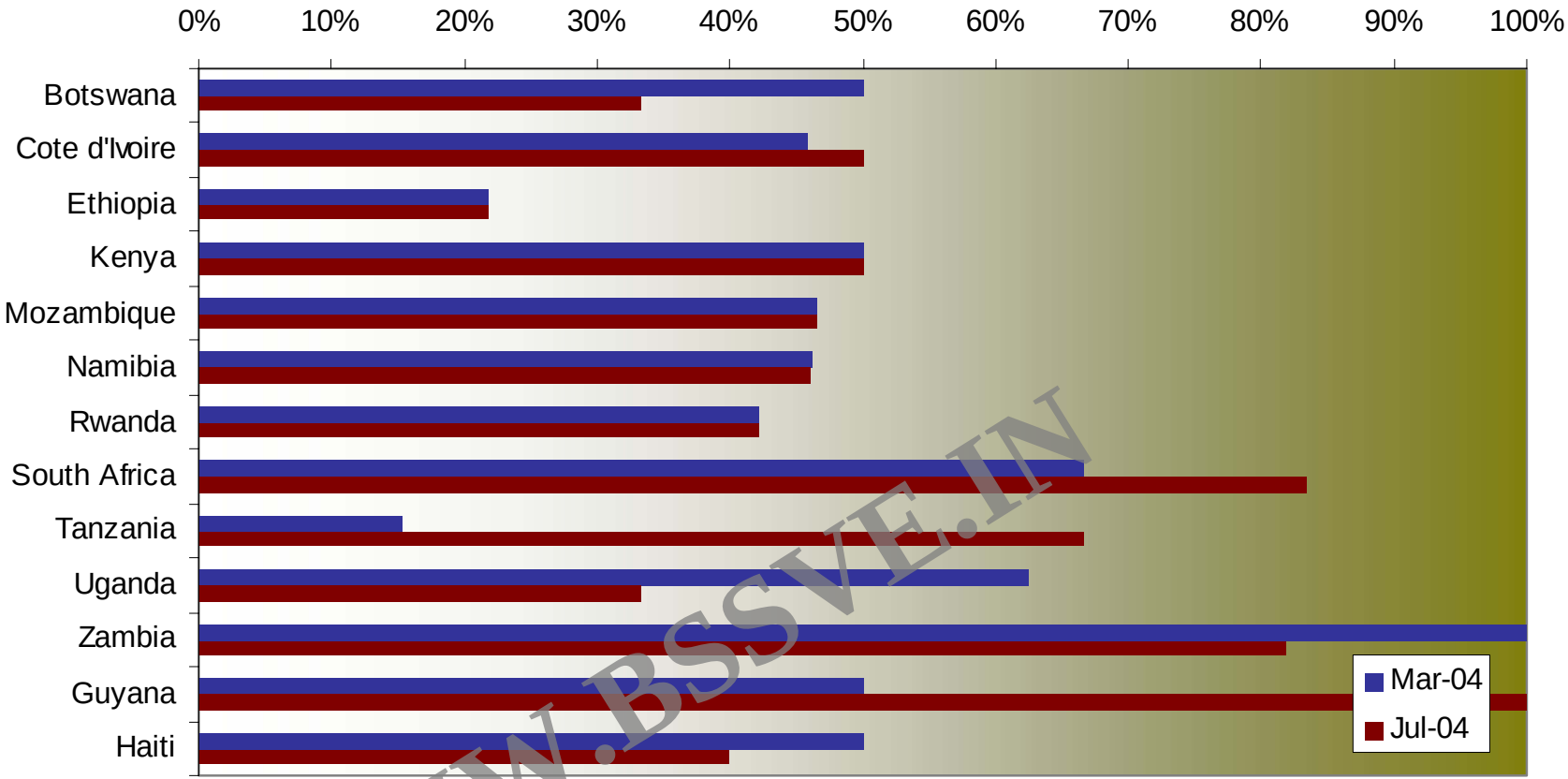
Country Consistency with WHO 2003 Recommendations for Adult ART Guidelines



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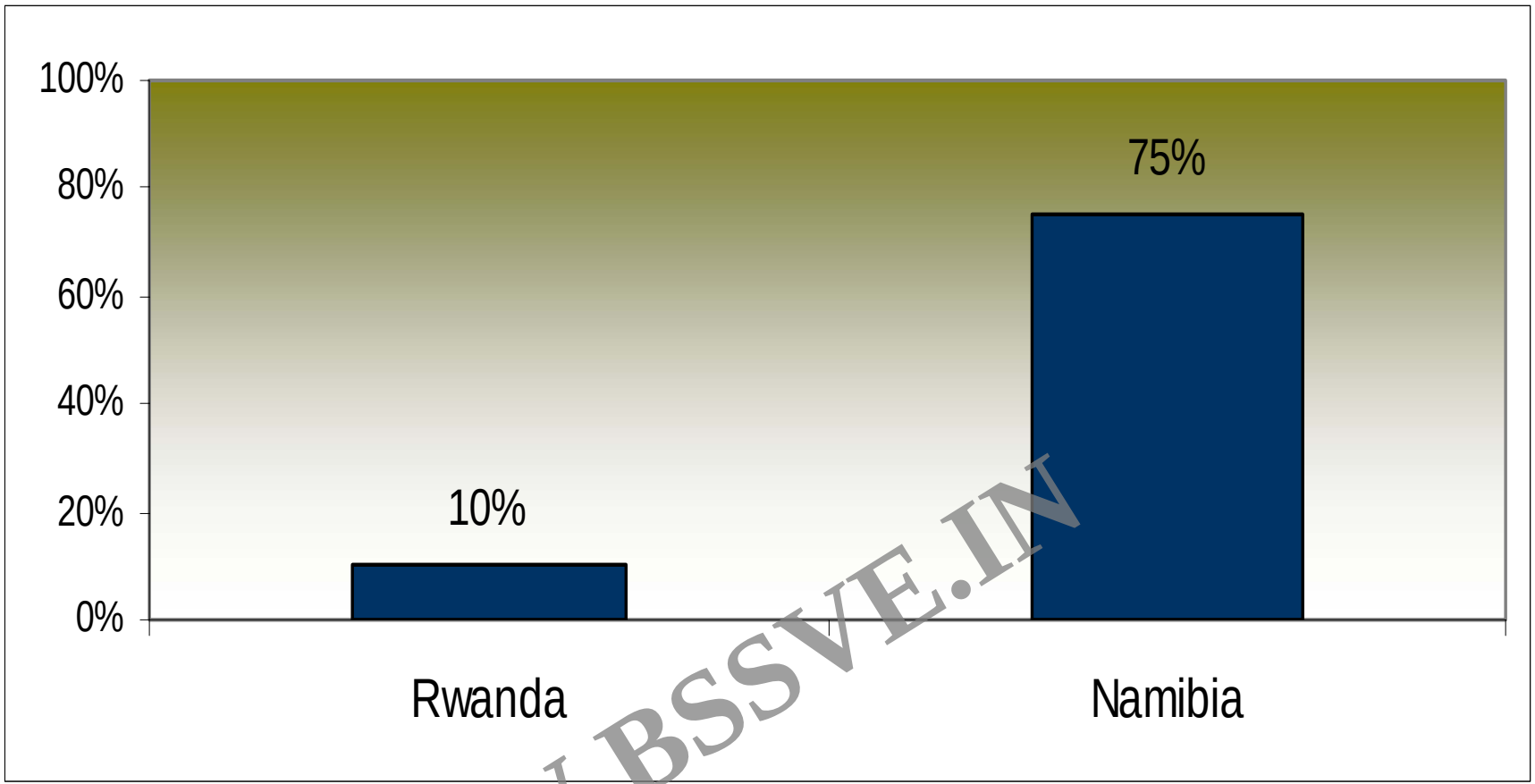
ART Guidelines Available – Rwanda and Namibia



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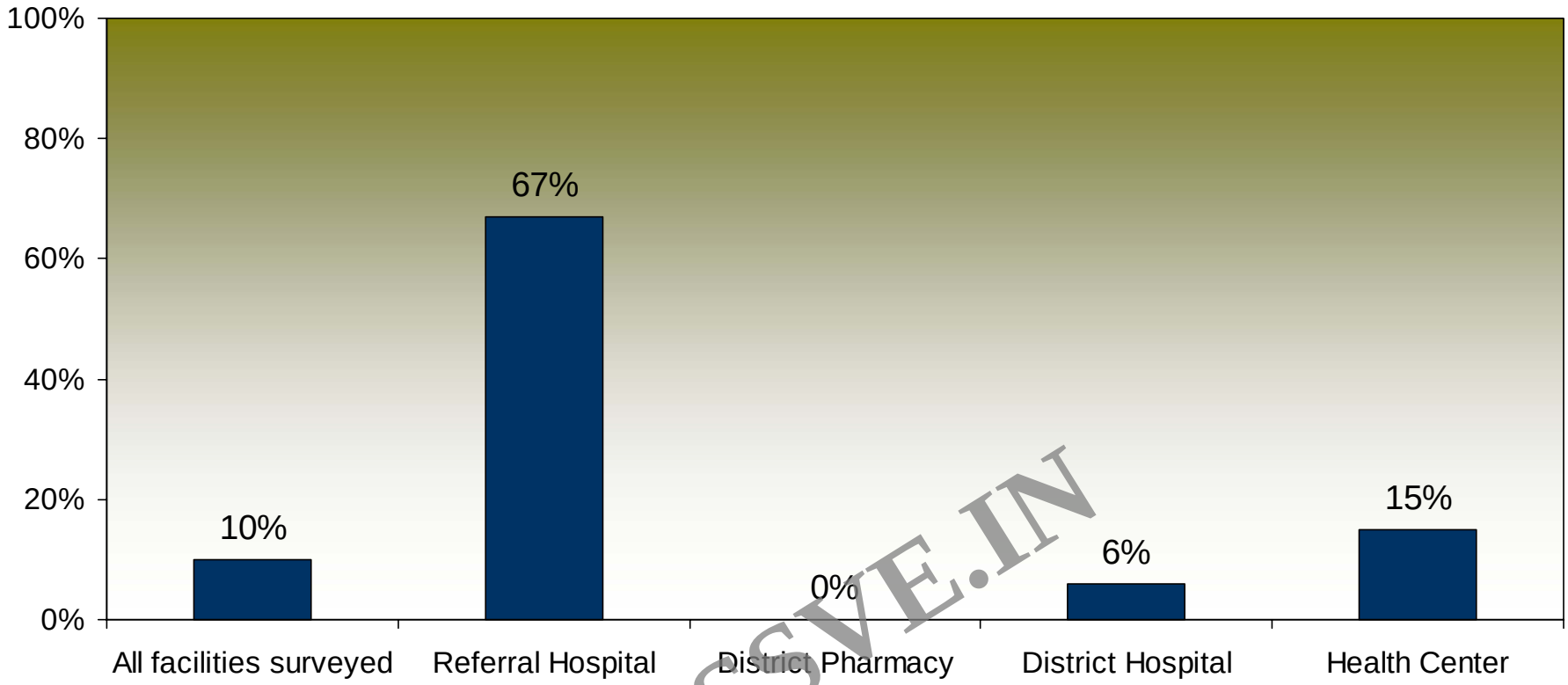
ART Guidelines in Health Facilities - Rwanda



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Complexities in Establishing and Implementing STGs for HIV/AIDS (1)

- Multiple single agents and fixed-dose combinations
- Multiple regimens approved
- Differing laboratory monitoring capacities
- Differing and often weak pharmaceutical management capacities
- Different recommendations for special groups (e.g. pregnant women, children)
- Rapid change in recommendations due to treatment failure, drug resistance patterns, and/or new treatments becoming available
- Cost and logistics involved in changing from one regimen to another
- Need to mobilize both public and private sectors
- Non-pharmaceutical management and counseling issues

Why Are EMLs and STGs Not Followed?

- Do not reach the right people
- Pharmaceutical products available in facilities not on EML or STGs
- Lack of appropriate training in the use of STGs
- Lack of transparency during development process, which leads to the lack of credibility and acceptance
- Lack of involvement from respected members of the professional community
- Not based on adequate evidence
- Not current
- Not realistic – finances not available to purchase

Avoiding Failure

- Involve a wide group of experts
- Have a purpose and goals
- Gain official status
- Be open
- Have mechanisms for additions, revisions, and use of non-formulary drugs
- Obtain the support of professional organizations
- Use medical and pharmacy schools
- Have a launching campaign

Implementing STGs

- Disseminate printed reference materials
  - STGs manual, posters, training materials
- Official launch—Ministry of Health officials and opinion leaders
- Initial training
  - Vital to implementing STGs
  - Prior to actual start date
- Reinforcement training
- Monitoring adherence to STGs
- Supervision

Summary

- Essential medicines lists, formularies and standard treatment guidelines can have considerable impact if developed and used properly
- STGs can also be an expensive waste of effort
- With STGs, the processes of production and use are as important as the product

Session 11:
Access to Essential Medicines

Keith Johnson

Management Sciences for Health

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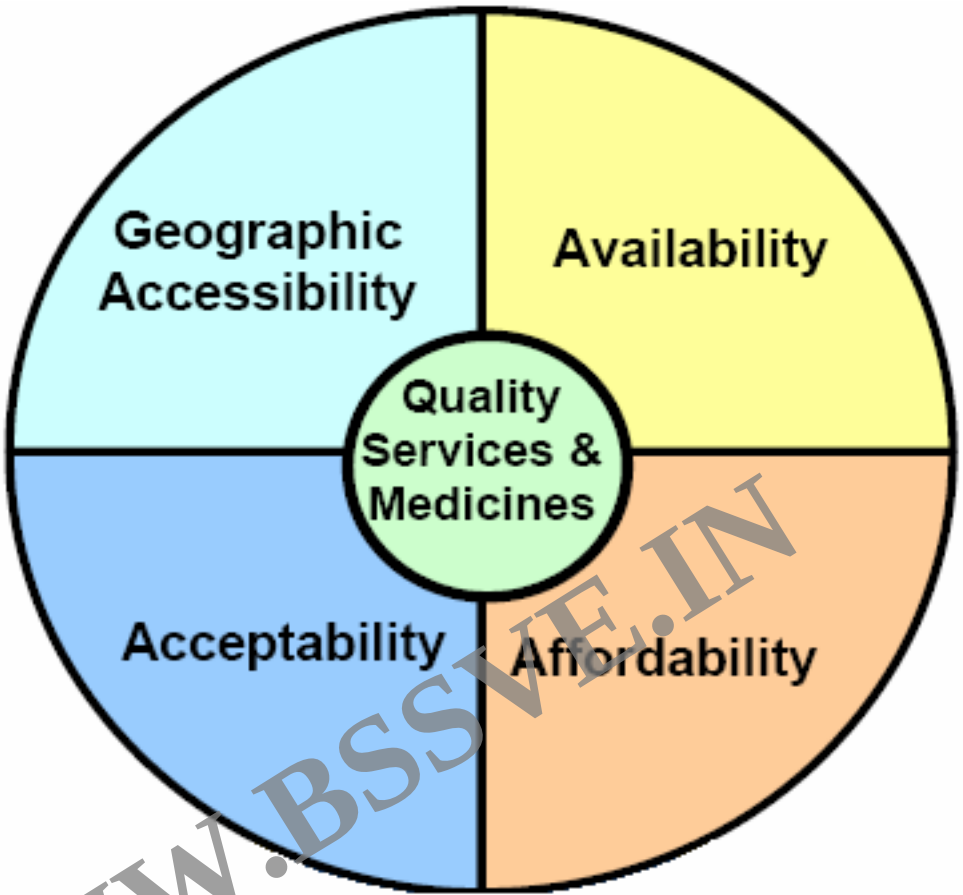
Unit Objectives

1. Understand the different dimensions of access
2. Explain how to appraise access to essential drugs at the community level
3. Describe different types of community participation that affect access
4. Describe how to do a community needs assessment
5. Describe recent innovations to improve access involving the private sector
6. Expand the main factors influencing cost, use, and access to pharmaceuticals

What Is Access to Medicines?

- Access: “potential”use (freedom or ability to obtain a medicine)
- Use: “accomplished”access “exercised”(freedom or ability to utilize obtained medicine)
- Medicinal products or services may be accessible (available, affordable, etc.) but not necessarily used

Framework for Assessing Access to Medicines



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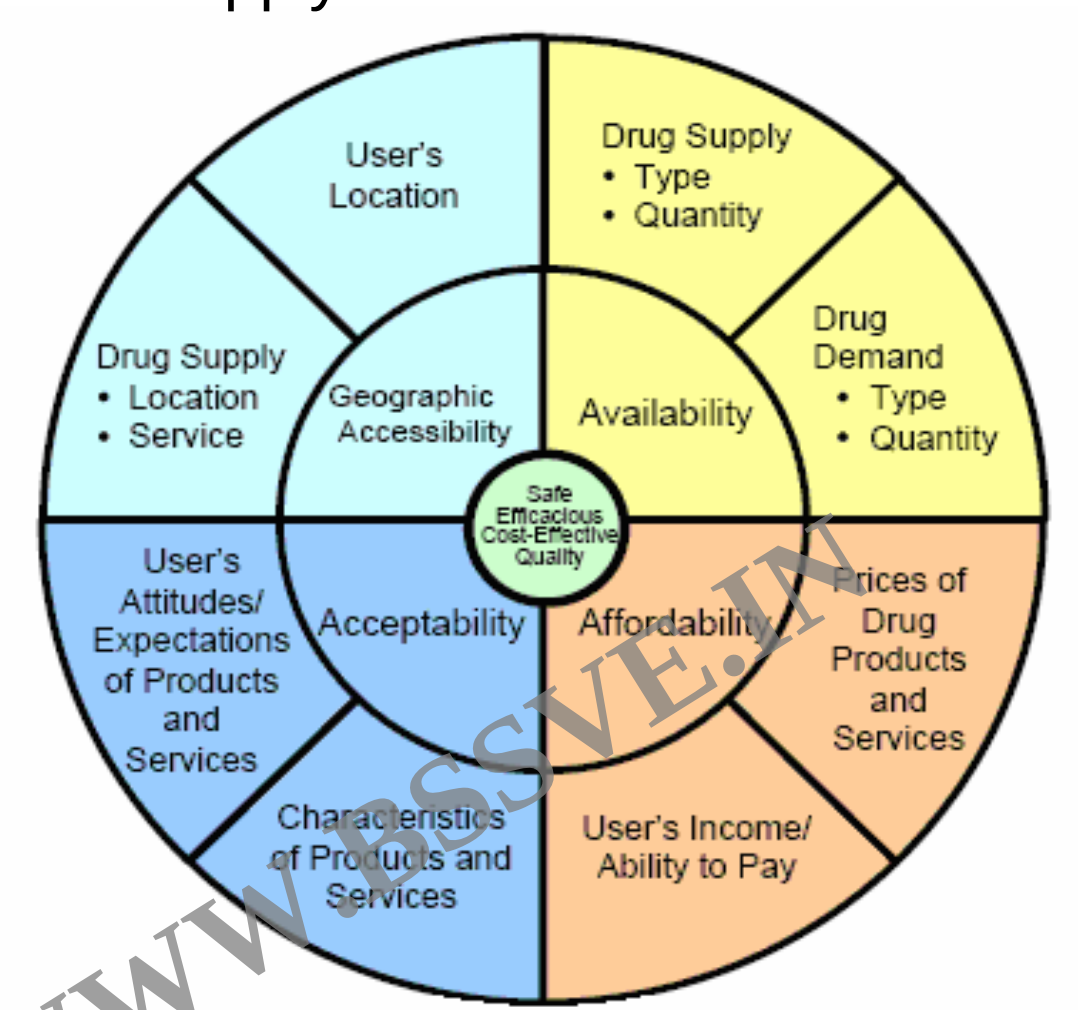
Framework for Assessing Access to Medicines

Supply and Demand Factors



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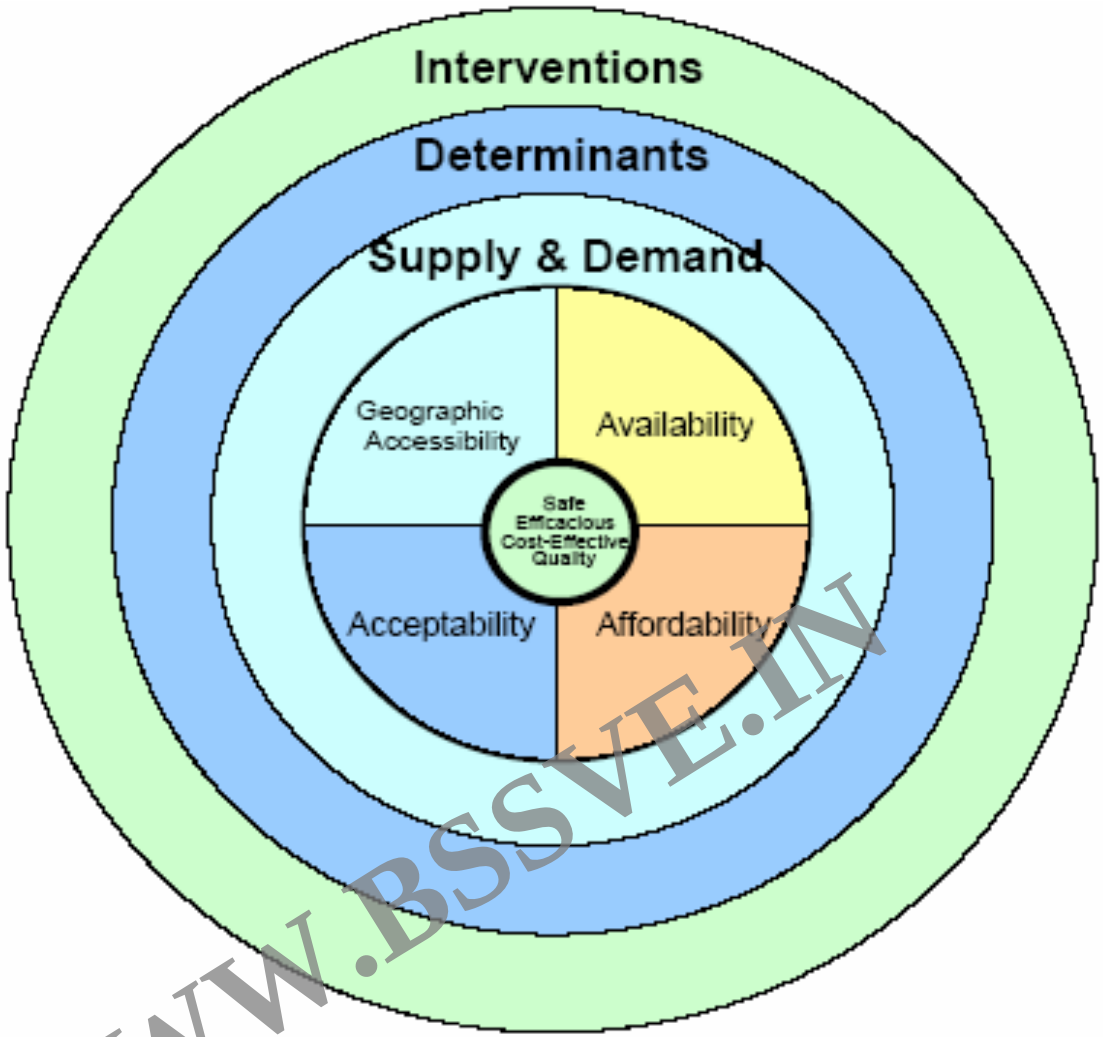
Framework for Assessing Access to Medicines



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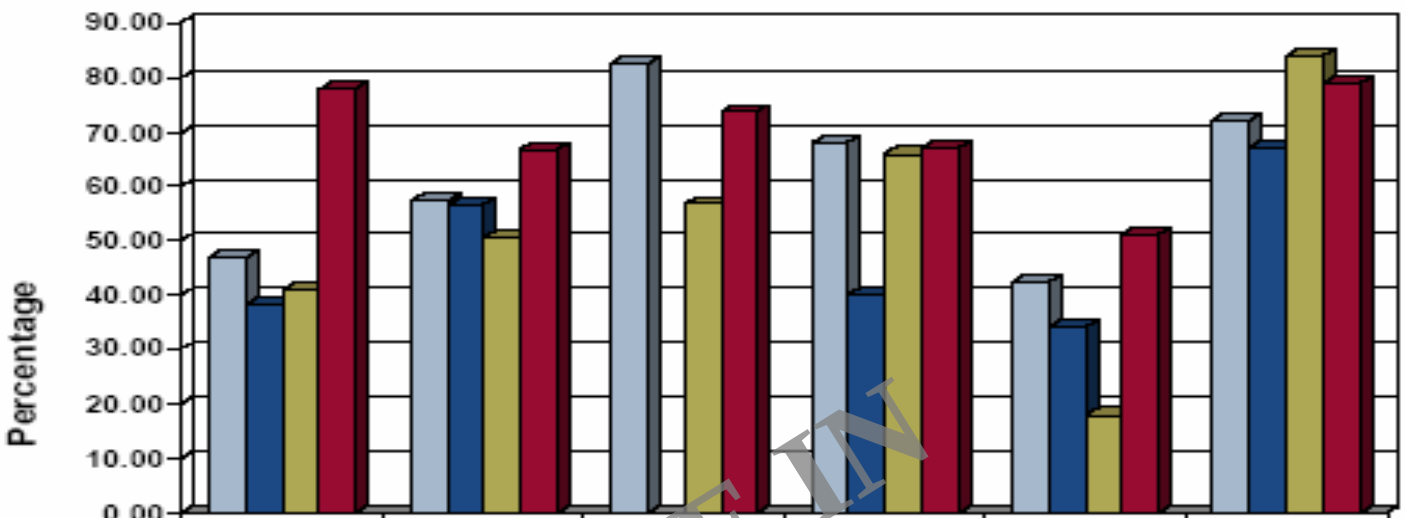
Availability

- Relationship: Supply vs. demand
- Determinants:
  - Inadequate forecasting of needs, procurement practices, manufacturing capacity
  - Demand for alternative products, etc.
- Interventions:
  - Essential medicines list
  - pooled procurement

Availability: Selected Countries



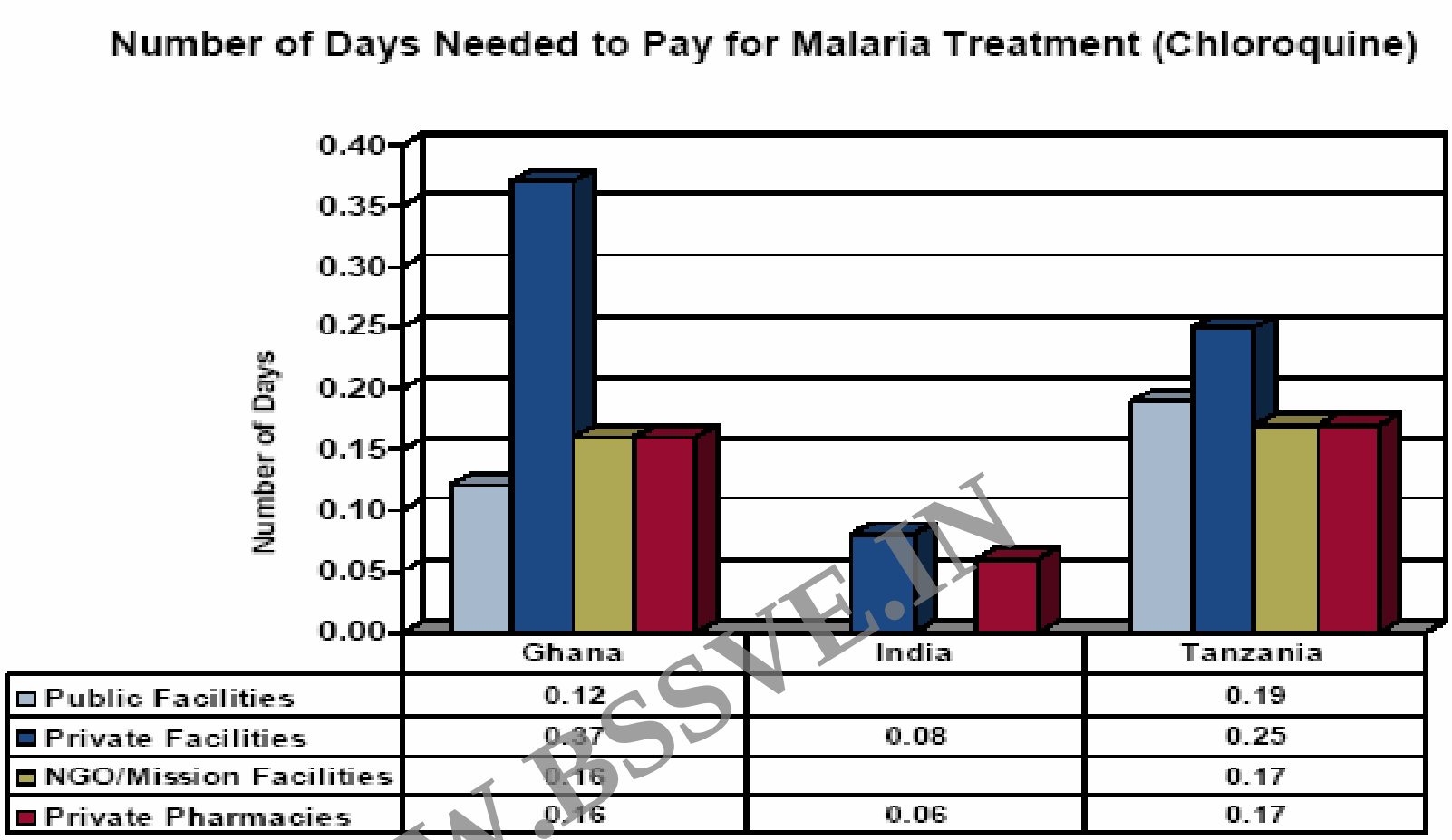
	Brazil	Cambodia	El Salvador	Ghana	India	Tanzania
Public Facilities	46.90	57.29	82.49	68.00	42.60	72.00
Private Facilities	38.10	56.42		40.00	34.30	67.00
NGO/Mission Facilities	41.00	50.35	56.75	66.00	18.00	84.00
Private Pharmacies	78.00	66.82	73.70	67.00	51.00	79.00

Source: MSH: Management Sciences for Health. Used with permission.

Affordability

- Relationship: Price, cost, value vs. user's income or ability to pay
- Determinants:
  - Lack of product competition
  - Unemployment or level of income
- Interventions:
  - Generic or therapeutic equivalence policies
  - Social insurance, income generation measures

Affordability: Ghana, India, Tanzania

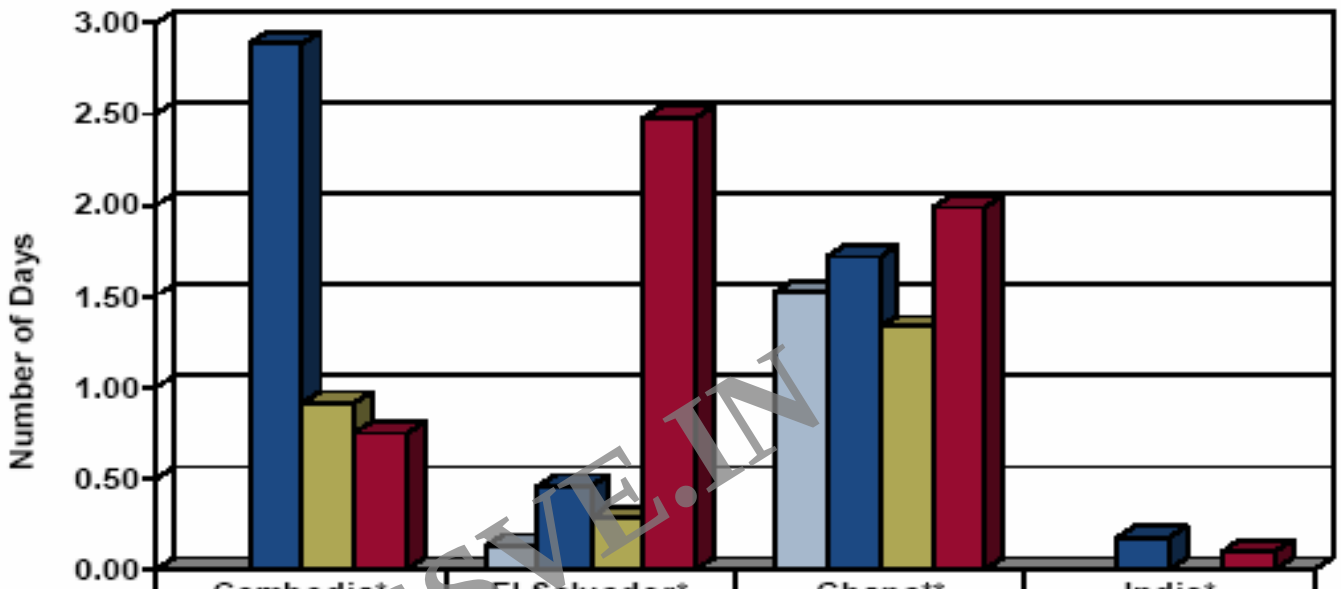


	Ghana	India	Tanzania
Public Facilities	0.12		0.19
Private Facilities	0.37	0.08	0.25
NGO/Mission Facilities	0.16		0.17
Private Pharmacies	0.16	0.06	0.17

Note: For Tanzania – Sulfadoxine + Pyrimethamine

Source: MSH: Management Sciences for Health. Used with permission.

Affordability: Cambodia, El Salvador, Ghana, India



	Cambodia*	El Salvador*	Ghana**	India*
Public Facilities		0.13	1.52	
Private Facilities	2.89	0.45	1.72	0.17
NGO/Mission Facilities	0.91	0.28	1.33	
Private Pharmacies	0.75	2.48	1.99	0.09

*Child 1–5 years old, co-trimoxazole; **Adult, amoxicilline

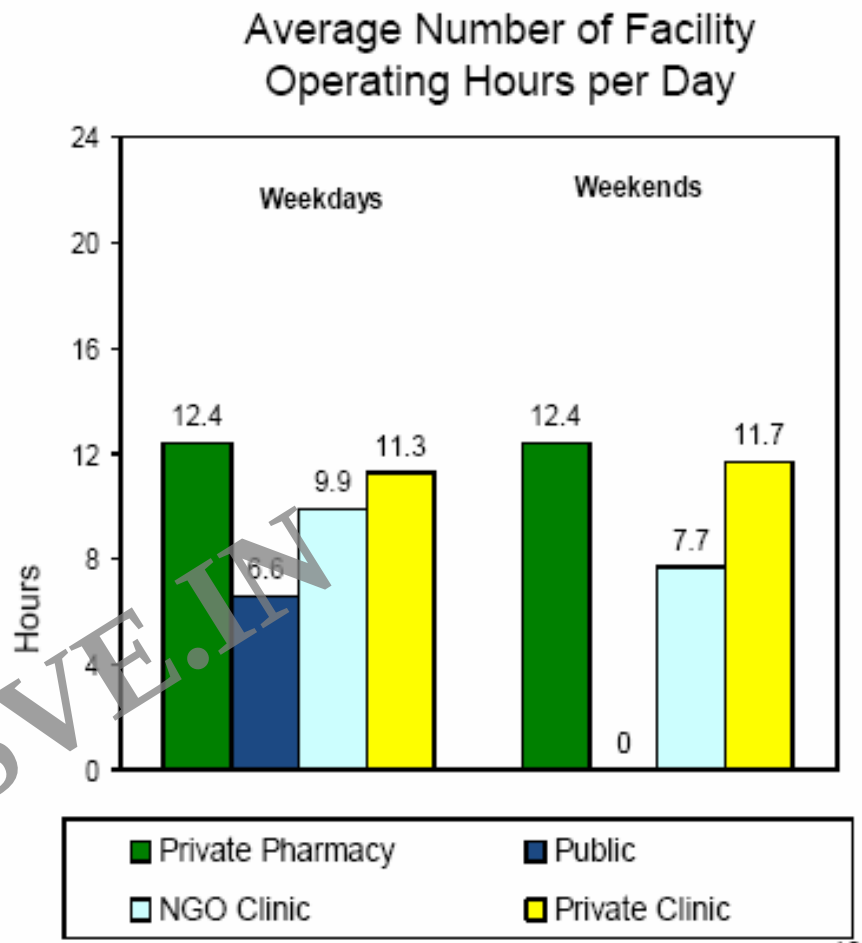
Source: MSH: Management Sciences for Health. Used with permission

Geographic Accessibility

- Relationship: Location of supply or services vs. location of user
- Determinants:
  - Insufficient economic incentives to operate retail drug outlets
- Interventions:
  - “Rural drug outlet” program
  - “Pharmacy franchise” program

Geographic Accessibility: Cambodia

- 35% of the population is more than 10 km or 2 hours'walk away from any basic health care facility



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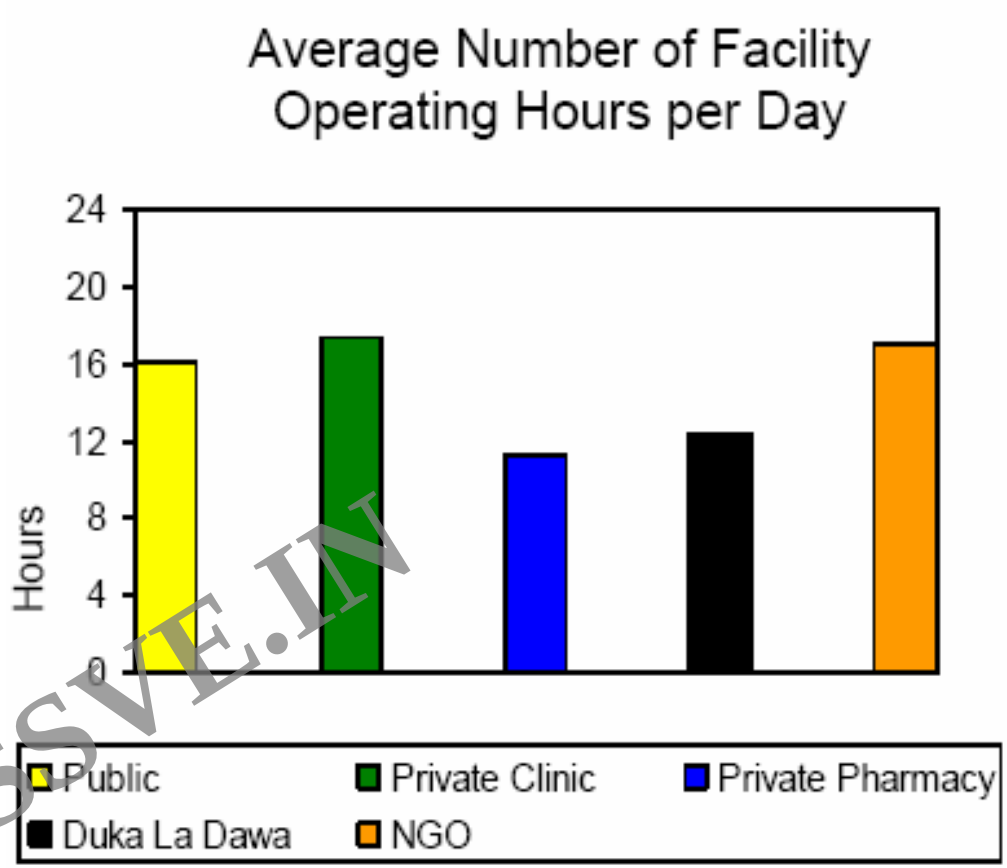
Geographic Accessibility: Tanzania

Distance to Health Facility

- 14% of the population is more than 10 km away from public facility
- 6% is more than 10 km away from private drug retailer



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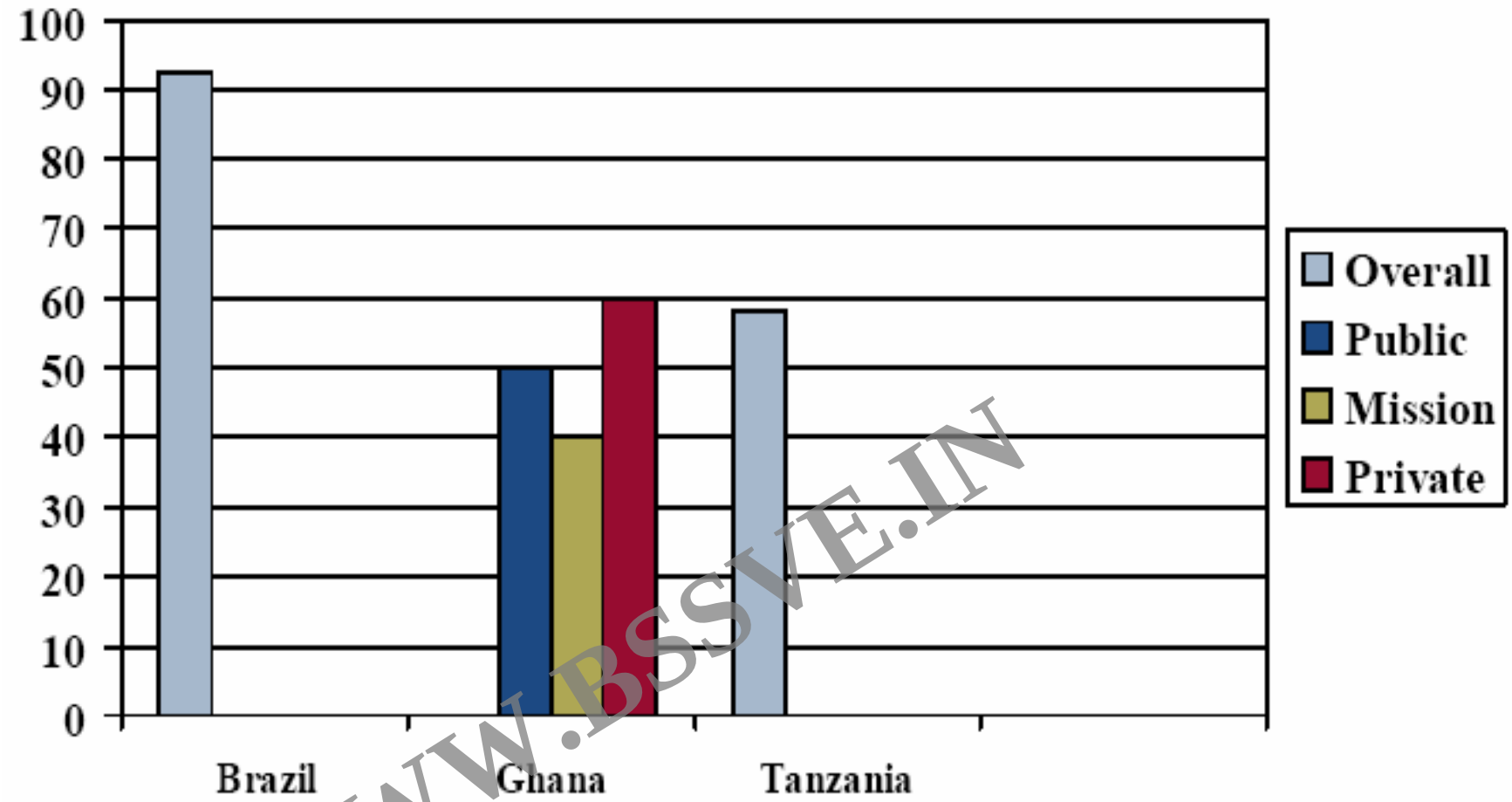
Acceptability

- Relationship: Characteristics of products and services vs. user's attitude toward, perception of, or expectations of products and services
- Determinants:
  - Product appearance (color, container)
  - Information (pharmaceutical equivalence, indications, instructions)
- Interventions:
  - Product change
  - Information program
  - Customer service improvements

Acceptability/Satisfaction



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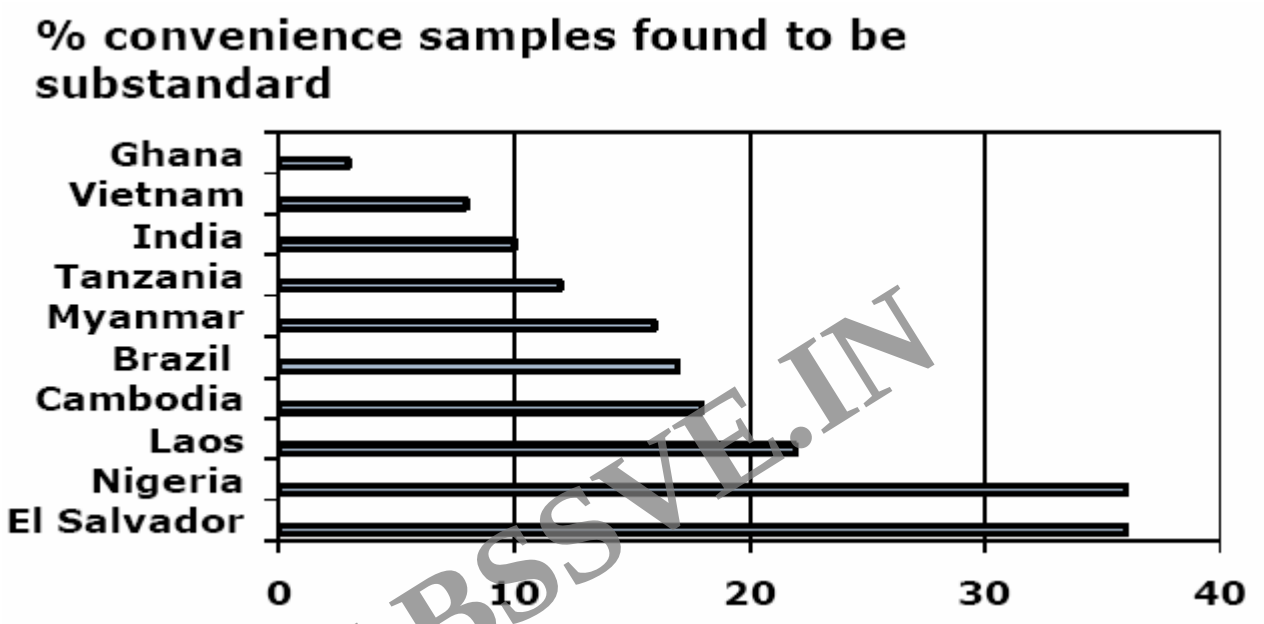
Product Quality

Unreliable Medicine Quality –3 to 36 % of samples are substandard; a health hazard



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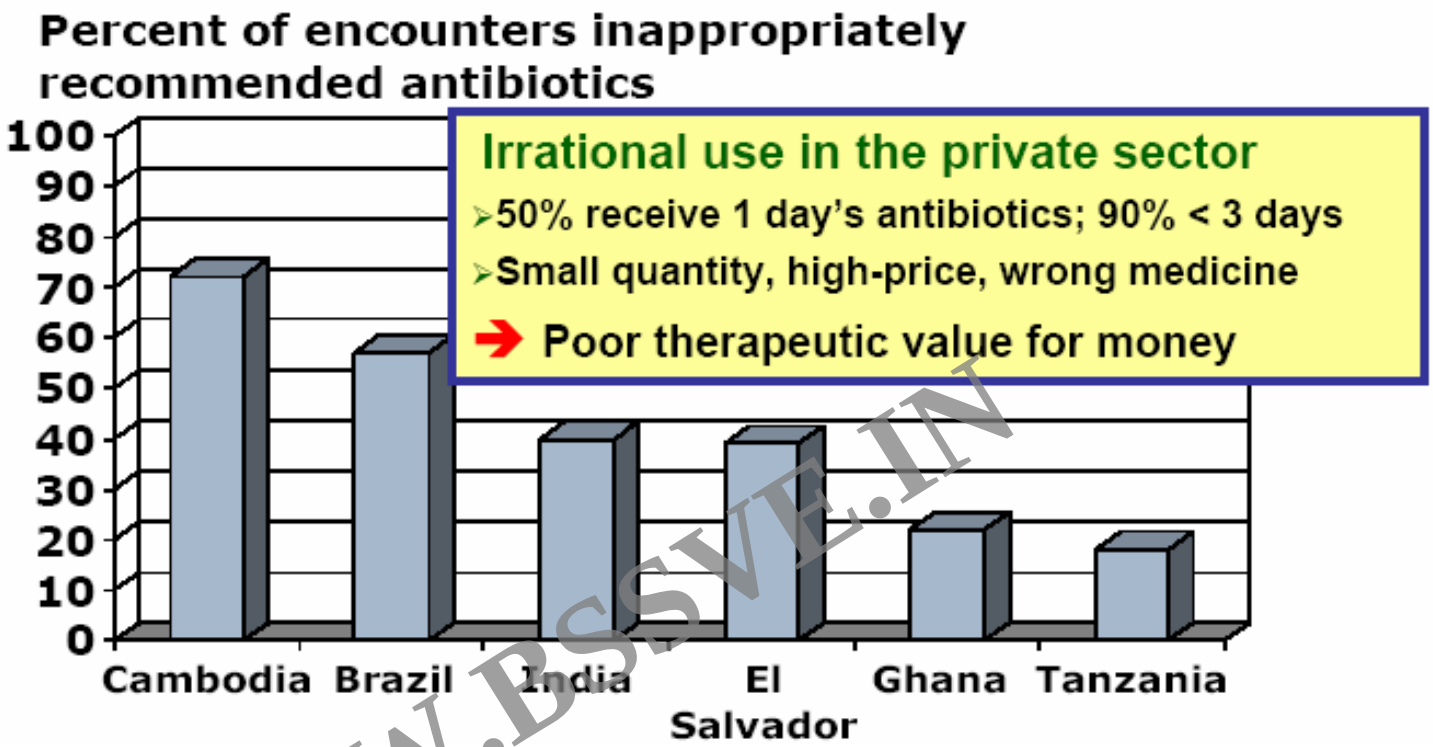
Service Quality

18 to 72% of antibiotics are inappropriately recommended



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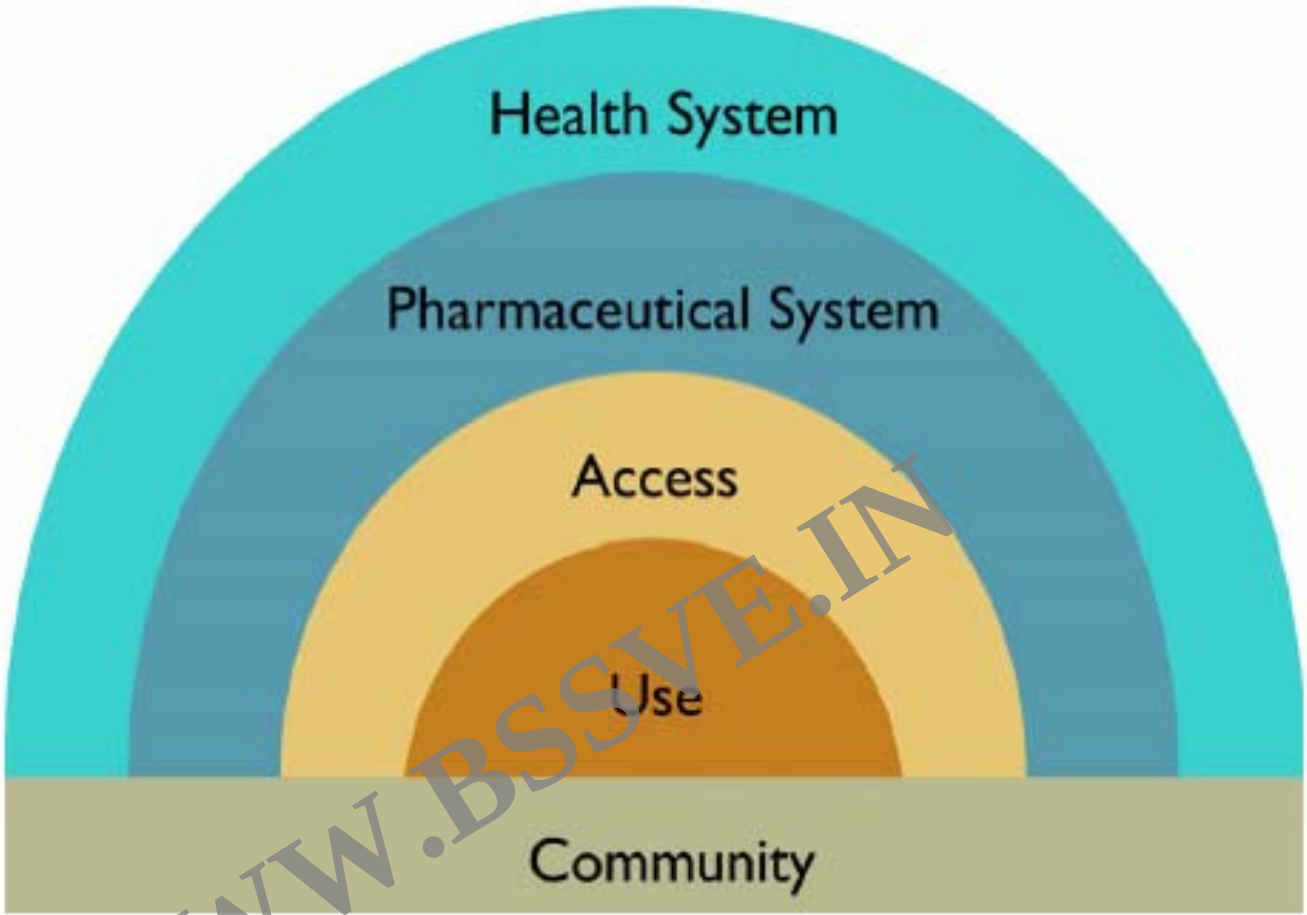
Designing and Implementing Interventions

- Intervention should address identified access gaps
- Multifaceted targeting of different barriers is more likely to succeed than single interventions
- Evaluation of impact is essential

Pharmaceutical Management, Access, and Use of Medicines



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Available Methods and Indicators

- Indicators for monitoring national drug policies
- Operational package for monitoring and assessing the pharmaceutical situation in countries
- Access indicators
- Price monitoring
- Logistics assessment indicators
- Pharmaceutical supply systems assessments
- Studies of drug use in health facilities
- Studies of drug use in communities

Tanzania

Demographics	Tanzania
Area (sq km)	945,100
Population	32,900,000 25% urban
GNP per capita	USD 240
Human Development Index	0.358 (150/174)
Literacy rate	Male: 84% Female: 65.7%
Infant mortality rate	94.8 per 1,000
Life expectancy	47 years

Strategies to Improve Access in Tanzania

Gaps	Interventions
Availability, especially in public sector	Approving additional sources of supply to Medical Stores Department for public sector
Accessibility –14% more than 10 km of public facility; 6% more than 10 km of private drug retailer	A regulated network of accredited drug dispensing outlets (ADDOs)
Quality and affordability of products and services, especially in the private sector serving rural areas	A quality assurance strategy to permit improved screening of drugs entering and circulating in the market

Where Do Tanzanians Buy Their Medicines?

- 339 Part I drug outlets (pharmacies)
- More than 4,000 Part II drug shops (*dukala dawa baridi* [DLDB])
- Population is largely rural; only 17% have access to private pharmacies
- DLDB shops more accessible to population than all other public or private drug outlets

Drug Outlets Per Capita
Population: 33.97 million

	# Facilities	Facilities per Capita
Part II shops (DLDB)	4,627	7,343
Public facilities	2,907	11,687
Voluntary/ religious	772	44,009
Private	934	36,375
Private pharmacies	339	102,026
Parastatal	211	161,017

So Where Do We Target Drug Access Interventions?

Sutton's corollary: <u>Go where the people go</u>

- Public sector (rarely over 25% of encounters)
- Mission/faith-based/NGO sector (up to 40% in rural areas)
- Traditional medicine (high usage in some areas)
- Private commercial sector (40–60% of encounters)

Tanzania Drug Shops –*Dukala Dawa Baridi* or "Cold" Drug Shops

Most geographically accessible and the first stop for over 60% of population for accessing medicines

Source: MSH: Management Sciences for Health. Used with permission.

Tanzania Drug Sellers –The Problem

- Unqualified, untrained staff
- Unknown drug quality

- Unreliable source of drugs
- High drug prices
- Inadequate regulation
- Insufficient variety of legally available drugs

Source: MSH: Management Sciences for Health. Used with permission.

Tanzania Drug Sellers –The Strategy

- *Dukala Dawa Muhimu* (essential drug shops)
- Accredited Drug Dispensing Outlets (ADDOs)
- TFDA regulations and standards of practice
- Training (both business and dispensing skills)
- Incentives (loans, mentoring, expanded list of legally sold drugs, marketing)
- Regulation and inspection – Local strategy
- Drug supply – Local sources; TFDA approved products

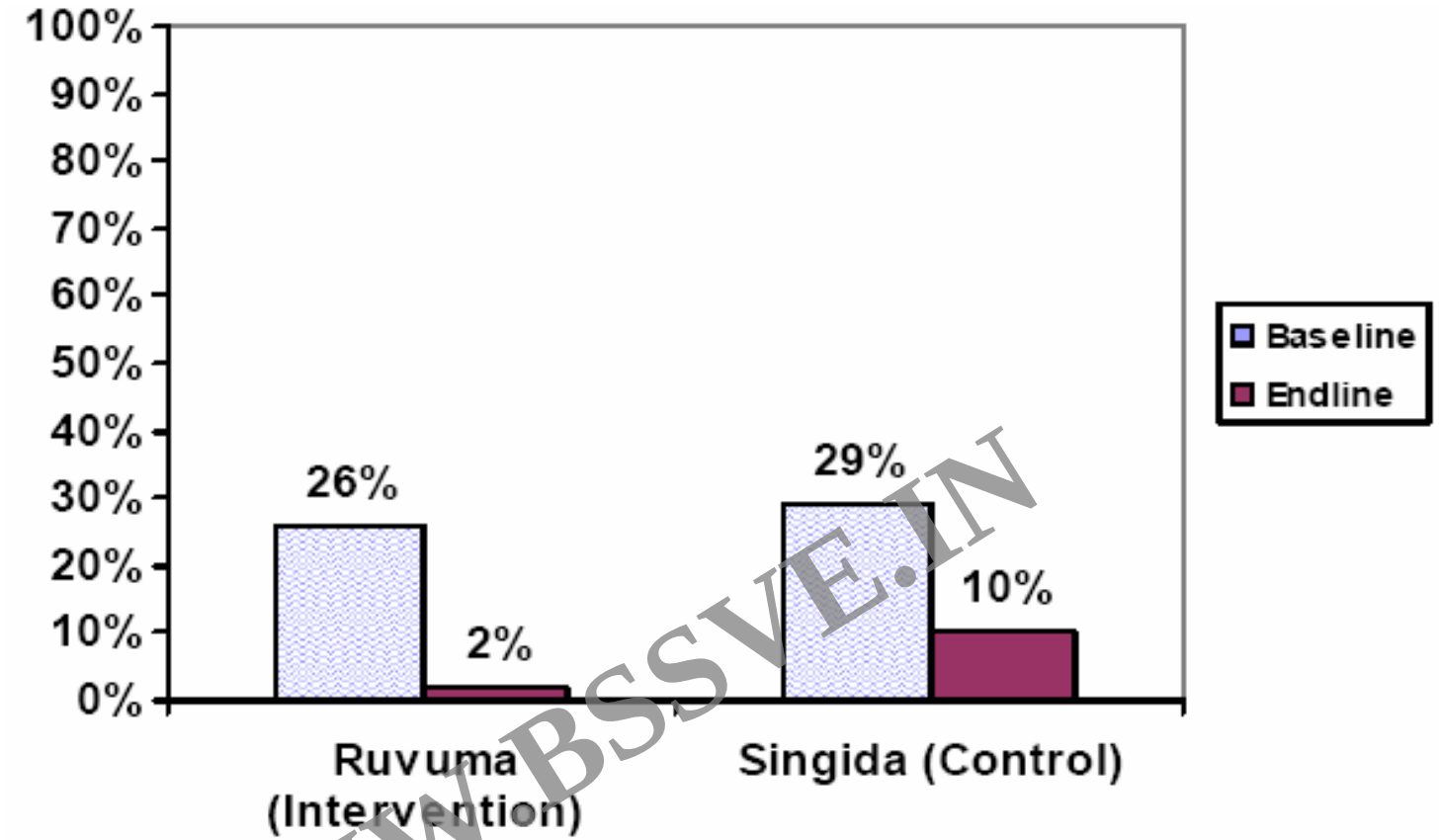
Tanzania Drug Sellers –The Results

Accessibility – 156 ADDO shops are open, with 36 applications pending (80 originally targeted); evaluated using the Singida Region as control

Source: MSH: Management Sciences for Health. Used with permission.

Product Quality

People in intervention group have a 1 in 50 chance of buying an unapproved drug, compared to a 1 in 10 chance in control group



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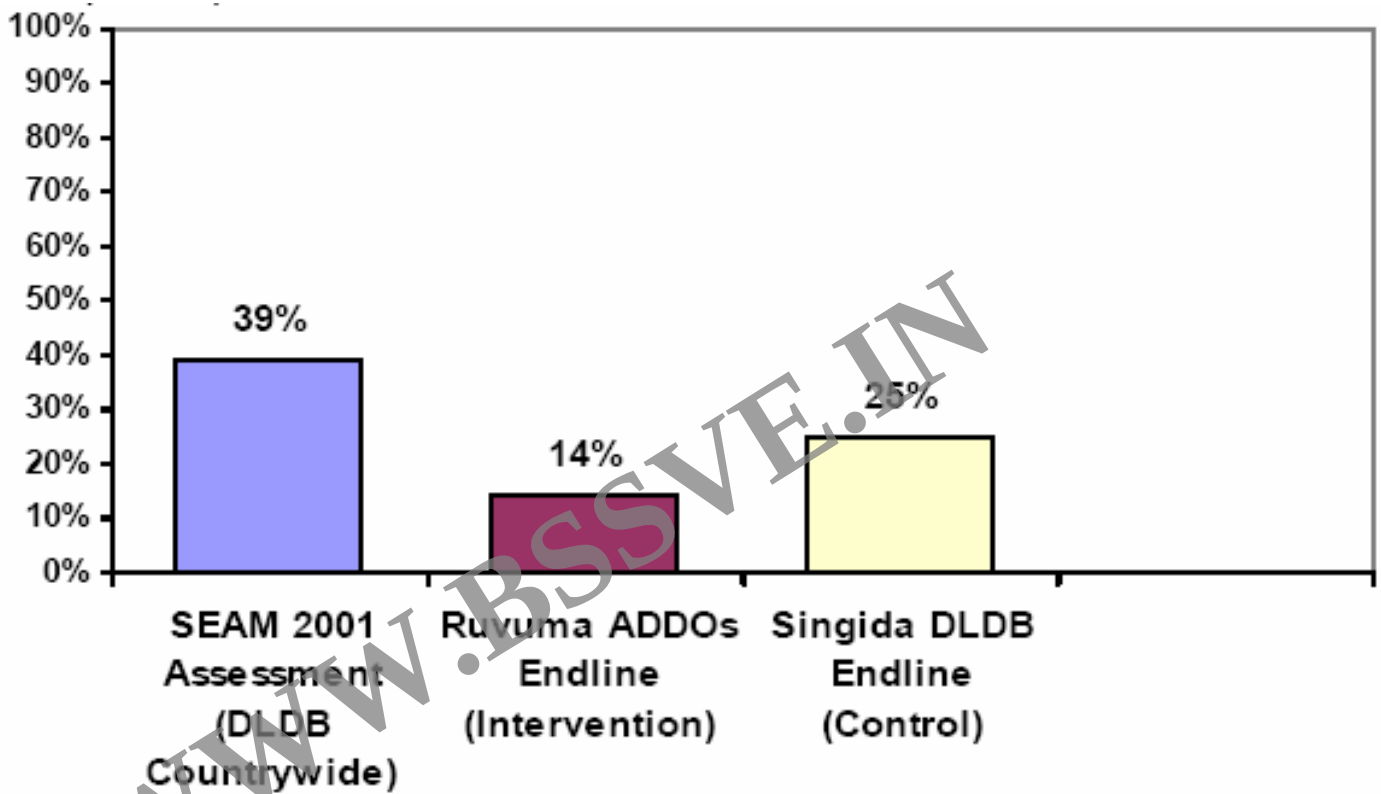
Service Quality

Fewer ADDO attendants (14%) sold/recommended antibiotics for URTI in intervention group at endline than during nationwide assessment (39%) or in control group at endline(25%)



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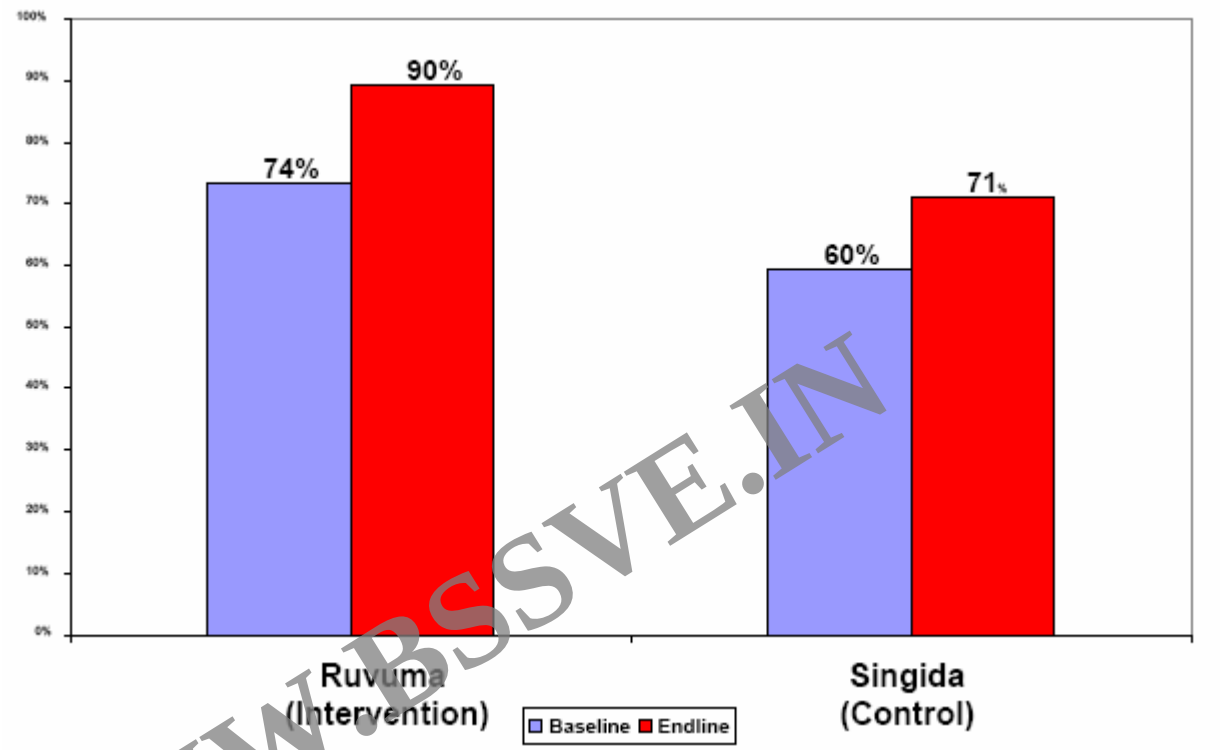
Availability

In intervention group, average availability of antimalarials increased from 74 to 90% vs. 60 to 71% in control region



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Affordability

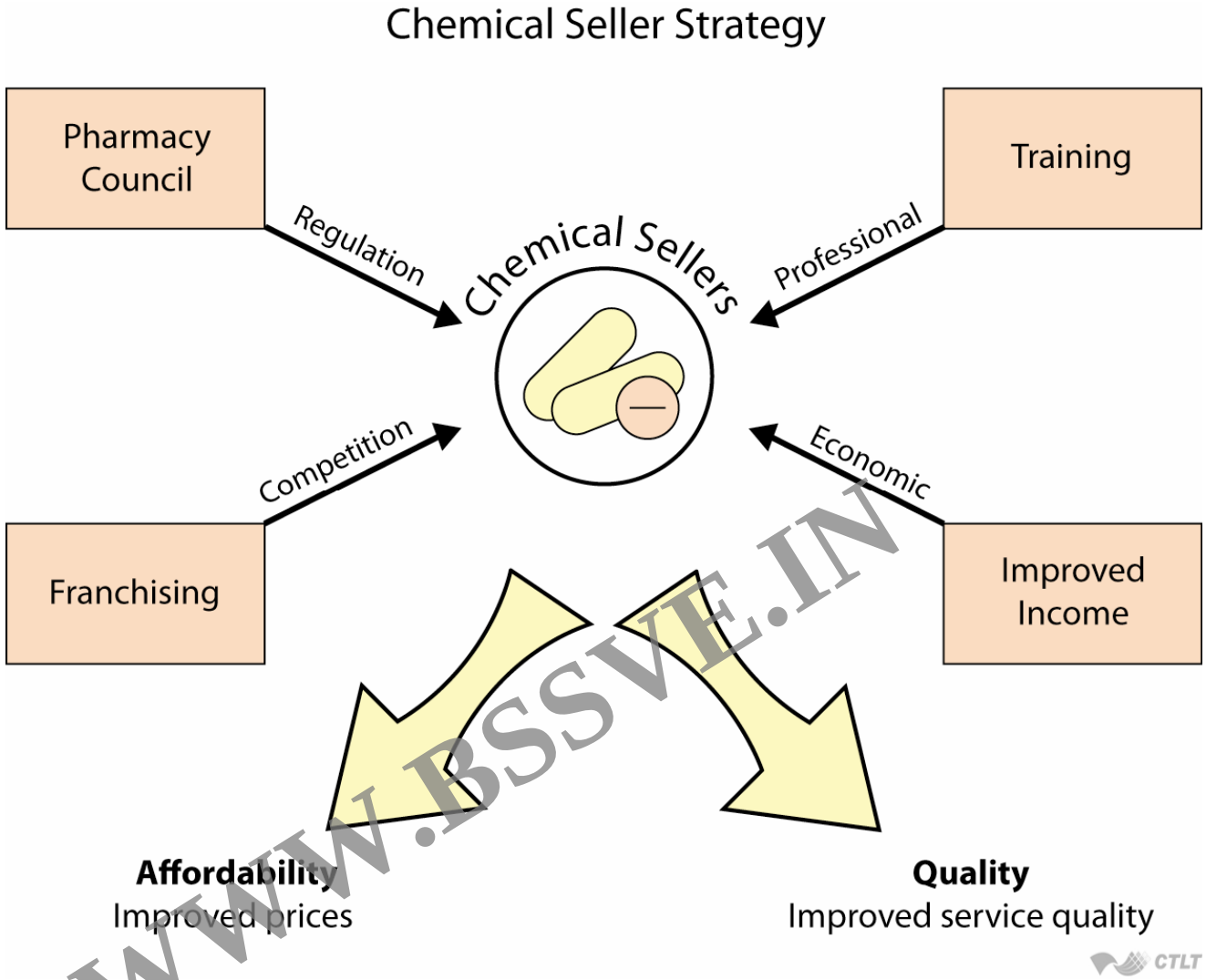
Average median prices increased slightly from baseline to endline in both intervention and control groups

- Prices in Ruvuma are now more in line with national market prices; tracer item prices same in both regions at end-line
- Median cost of course of treatment for malaria and URTI was better in intervention group60% less for malaria (TSH 200 in Ruvumavs. TSH 500 in Singida)10% less for URTI (TSH 900 in Ruvumavs. TSH 1000 in Singida)
- Customer base remained stable in intervention group

Tanzania Drug Sellers –The Future

- National roll-out
  - Government of Tanzania buy-in; funding
  - USAID support for 2 initiatives; other donors
- Expanded services (e.g., child health, HIV/AIDS, malaria)
- Next steps:
  - Developing and testing roll-out strategies; coordination of donors
  - Refinement of training, supervisory, and inspection roll-out strategy and support
  - Roll-out sustainability with continuing government and donor commitment

Chemical Sellers Intervention in Ghana



Ghana Chemical Sellers –The Strategy

1. CAREshop®chemical sellers franchise
   - For-profit franchisor (GSMFEL); business plan
   - Conversion/upgrading of selected LCS shops
   - 5-week training; ongoing mentoring/supervision
   - Pooled procurement and supplier negotiation
   - Central marketing/promotion;
   - CAREshopline
2. Regulation and supervision
   - Pharmacy Council
   - Franchisor supervisory visits (monthly)

Ghana Chemical Sellers: The Results

Accessibility–263 CAREshops are open (250 originally targeted) with 40 more shops scheduled to open each quarter; evaluated against Licensed Chemical Sellers (LCS) in Eastern/Volta Regions and LCS in Western Region

Source: MSH: Management Sciences for Health. Used with permission.

Ghana Chemical Sellers: The Results

- Service quality: Mixed results
  - Increased antimalarial dispensing (50 to 62%) compared with 3% decrease in control; but only 18% dispensed exactly according to treatment guidelines
  - 59% of staff asked about malaria symptoms (50% baseline; 31 & 27% for controls)
- Availability: Slight decrease in tracer items
- Affordability: Slight increase; median price 3% less than Eastern/Volta region controls
- Sustainability: Breakeven point now at 600 outlets

Ghana Chemical Sellers: The Future

- GSMFEL committed to continued expansion
  - 600 outlets (rate of 40 per quarter)
  - Government support for roll-out and prioritization for donors
- Expanded public health services and products
- Next steps
  - Limited drug list, pooled procurement, and tendering/negotiations
  - Expanded line of CAREshopproducts
  - Control/recover costs of training and supervision
  - Investment capital/additional donor support for roll-out
  - Regional warehouses and operational facilities

Drug Seller Initiatives: The Models

Feature	Tanzania	Ghana	Kenya
Structure	Independent drug seller shops (ADDOs)	Franchised chemical seller shops	Franchised drug shops or clinics
Focus of control	Government accreditation and regulation	Franchiser	Franchiser
Shop selection	Conversion or new	Conversion	New
Operators	*Duka la dawa muhimu* trained drug sellers	Licensed chemical sellers	Community health workers or nurses
Training	Owners and dispensers – 5 weeks	Owners and assistants – 5 weeks	Owners and assistants – 4 weeks
Supervision	ADDO project support	Franchiser (monthly)	Franchiser
Inspection and regulation	Local inspectors linked to TFDA	Franchiser (monthly) + Pharmacy Council	Franchiser (monthly)

Drug Seller Initiatives: The Results

	Tanzania ADDOs	Ghana CAREshops	Kenya CFWshops
Business model viability	↑	↑	?
Product quality	↑	↔	↔
Service quality (rational use)	+/-	+/-	+/-
Affordability	↔	↔	↑
Availability	↑	↔	↔
Geographic accessibility	↑	↑	↑
Acceptability	↑	↑	↑
Government acceptance	↑↑	↑	↑

Drug Seller Initiatives: Lessons Learned

1. Both accreditation/regulation and franchise models appear to increase accessibility
   A. Country-specific determination
   B. Platform for expanded public health services
2. Training and supervision are key components but are complex and need to be made more economical
3. Harmonized and limited product lists, coupled with good forecasting and pooled procurement, are essential
4. The regulatory component, both internal and external, is critical to ensuring appropriate marketplace behavior
   A. Complex and requires resource commitment
   B. Decentralized regulation shows promise
5. Key stakeholder buy-in and participation are essential

Drug Seller Initiatives: Challenges

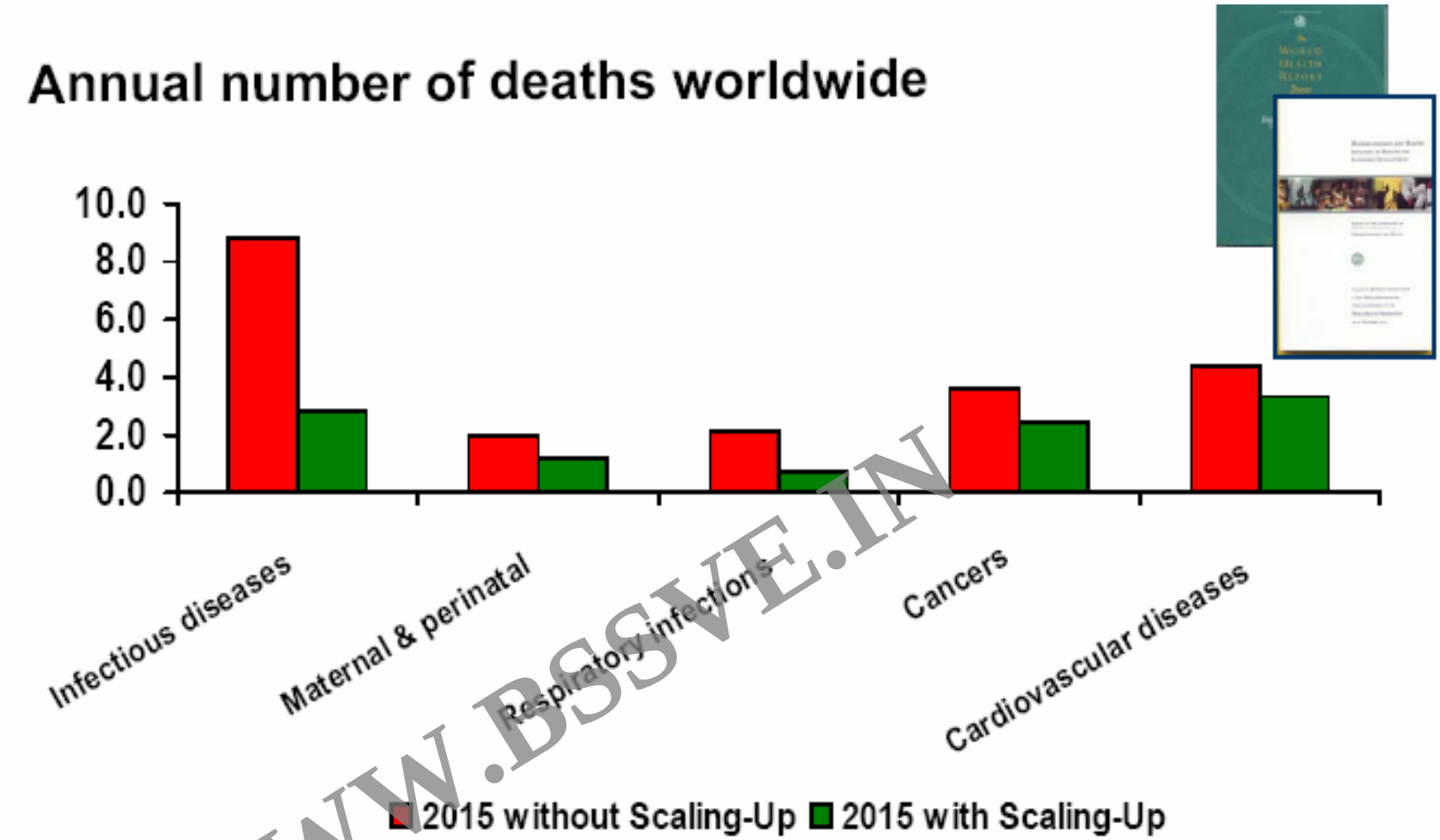
- Assuring public health focus and working with public health initiatives
  - Child Survival
  - Malaria
  - TB/HIV
- Managerial and financial sustainability when scaling up
- Ensuring local source of quality products and maximizing affordability
- Reaching the “poorest of the poor”

Access to Essential Medicines

"…25 years ago, less than half the world's population had regular ***access*** to essential drugs. Today, through a combination of public and private health systems, nearly two-thirds of the world's people are estimated to have access to full and effective treatment with the medicines they need. In absolute terms, the number of ***people with access*** to essential drugs grew from roughly 2.1 billion in 1977 to 3.8 billion in 1997."

Source: World Health Organization (WHO). 1998. *Revised Drug Strategy:WHO's Work in Pharmaceuticals and Essential Drugs.* EB/RDS/RC/1. Geneva, Switzerland: WHO.

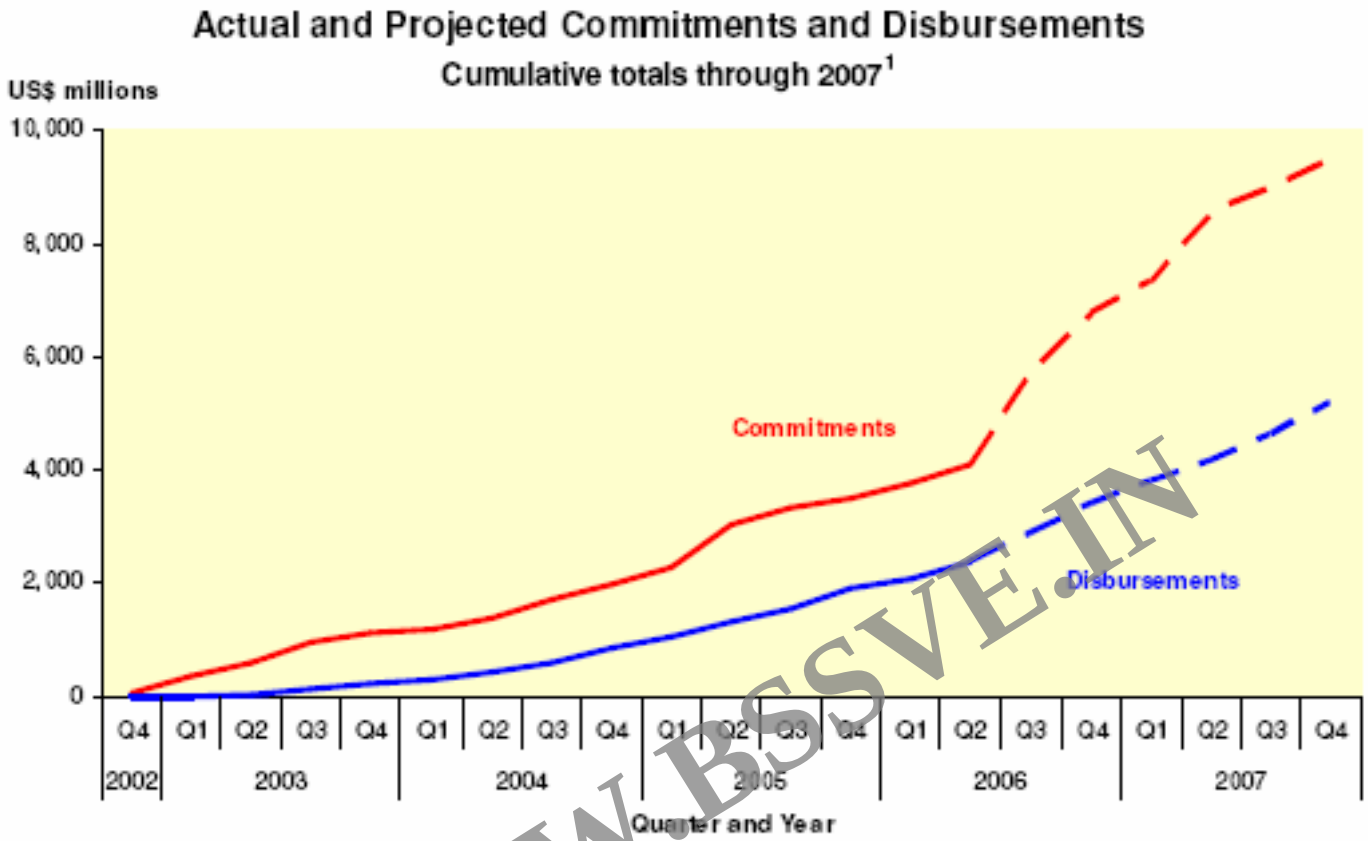
Access Gap – Scaling Up Existing Prevention & Treatment Would Save 10.5 Million Lives Per Year



Source: World Health Organization.

Implementation Gap

Technology & funding are vital –Scale-up is increasingly limited by inadequate existing public health delivery systems



[1] Assumes that Round 6 is approved in 2006 (at US$ 1.1 billion) and that Round 7 is approved in 2007 (at US$ 1.3 billion) for Phase 1 (years 1 & 2), and that renewal requests for Phase 2 (years 3 to 5) are approved when eligible. Incorporates assumptions regarding renewal rates, disbursement rates and other variables.

Commitments follow Board approvals and represent the full amount of the Global Fund's liability for the period of the grant agreement. For Phase 1, this period is the first two years of the grant's lifespan. In the case of Phase 2 grant agreements, this generally refers to years three to five of the grant's lifespan, although not all grants are for a five-year period.

Incremental ***disbursements*** of the approved grant are made periodically, not all at once, and so they lag somewhat behind commitments. As new rounds are approved and new grant agreements are signed, commitment and disbursement figures rise accordingly.

Source: Monthly Progress Update – 27 July 2006. The Global Fund to Fight AIDS, Tuberculosis, and Malaria. Used with permission.

Summary

- Access is a construct that encompasses various distinct dimensions
- The proposed analytical framework is useful to measure the various dimensions, identify determinants, and design interventions to improve access
- Experience with the use of proposed indicators is increasing
- We’ve got a long way to go to achieve universal access and equity

Session 1: Pharmaceutical Products and Under-served Populations

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Alan Lyles, Johns Hopkins School of Public Health

JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

USAID FROM THE AMERICAN PEOPLE

MSH MANAGEMENT SCIENCES for HEALTH

RPM Plus | Rational Pharmaceutical Management Plus

Overview of Course Sessions (1)

1. The global context of pharmaceutical products and underserved populations
2. International Policy and Legal framework
3. Drug manufacture, industrial pharmacy considerations, quality assurance and regulation
4. The Drug Management Cycle: Selection
5. Forecasting and Quantification
6. The Drug Management Cycle: Procurement
7. Drug Donations
8. The Drug Management Cycle: Distribution

Overview of Course Sessions (2)

9. The Drug Management Cycle: Use
10. Budgeting and Cost Control
11. Management Support Systems: Planning Cycle
12. Access to Essential Drugs
13. Pharmaceutical Care and Drug Utilization in an HIV/AIDS Clinic
14. Financing and Sustainability
15. Laboratory Exercise on Planning with an Emphasis on Budgets and Sensitivity Analysis
16. Student Presentations

"The right context is worth 50 IQ points."

-Alan Kay, Inventor of Object Oriented Programming & Laptop Computer Visionary

World Drug Purchases: Retail Pharmacies

IMS Health –Retail Drug Monitor: 12 Months to Sept 2005*

	Sept 2005	Sept 2004	% Growth US$	% Growth Constant Exchange
Selected World	365,348	341,483	7%	5%
North America	192,649	182,200	6%	5%
• USA	180,994	172,182	5%	5%
• Canada	11,656	10,017	16%	7%
Europe	90,685	84,132	8%	3%
• Germany	27,055	24,281	11%	7%
• France	22,639	20,641	10%	5%
• Italy	14,619	14,249	3%	(2%)
• UK	15,408	15,083	2%	(1%)
• Spain	10,965	9,879	11%	6%

Source: IMS Health, Retail Drug Monitor Sept 2005 in US$ millions.
www.imshealth.com/vgn/images/portal/cit_40000873/53/63/76322469IMS%20Retail%20Drug%20Monitor%20September2005.pdf

World Drug Purchases: Retail Pharmacies

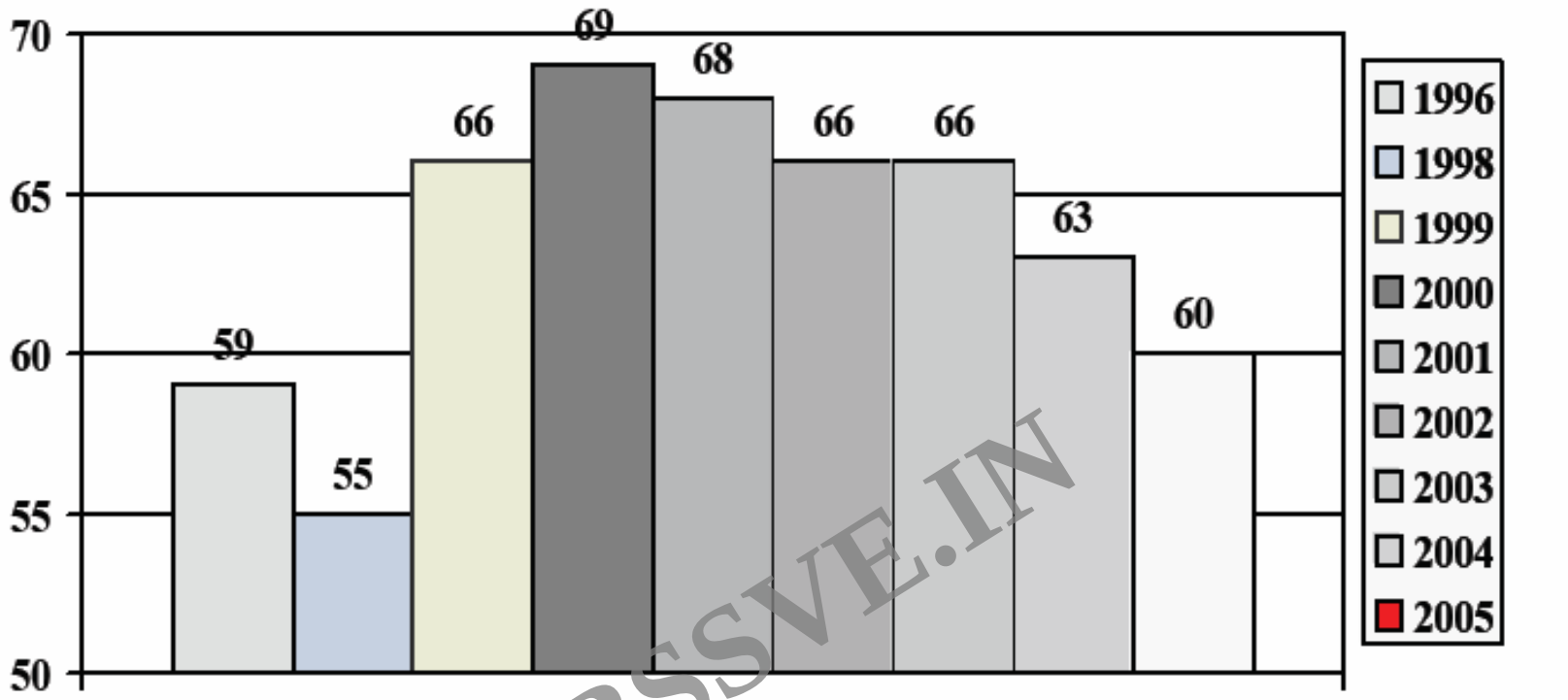
IMS Health –Retail Drug Monitor: 12 Months to Sept 2005*

	Sept 2005	Sept 2004	% Growth US$	% Growth Constant Exchange
Selected World	365,348	341,483	7%	5%
Japan*	60,820	57,122	6%	5%
Latin America†	15,524	13,935	20%	19%
• Mexico	7,184	6,338	13%	11%
• Brazil	6,369	4,844	31%	31%
• Argentina	1,971	1,752	13%	13%
Australia/NZ	5,670	5,094	11%	5%

*Including hospitals; †Leading three.

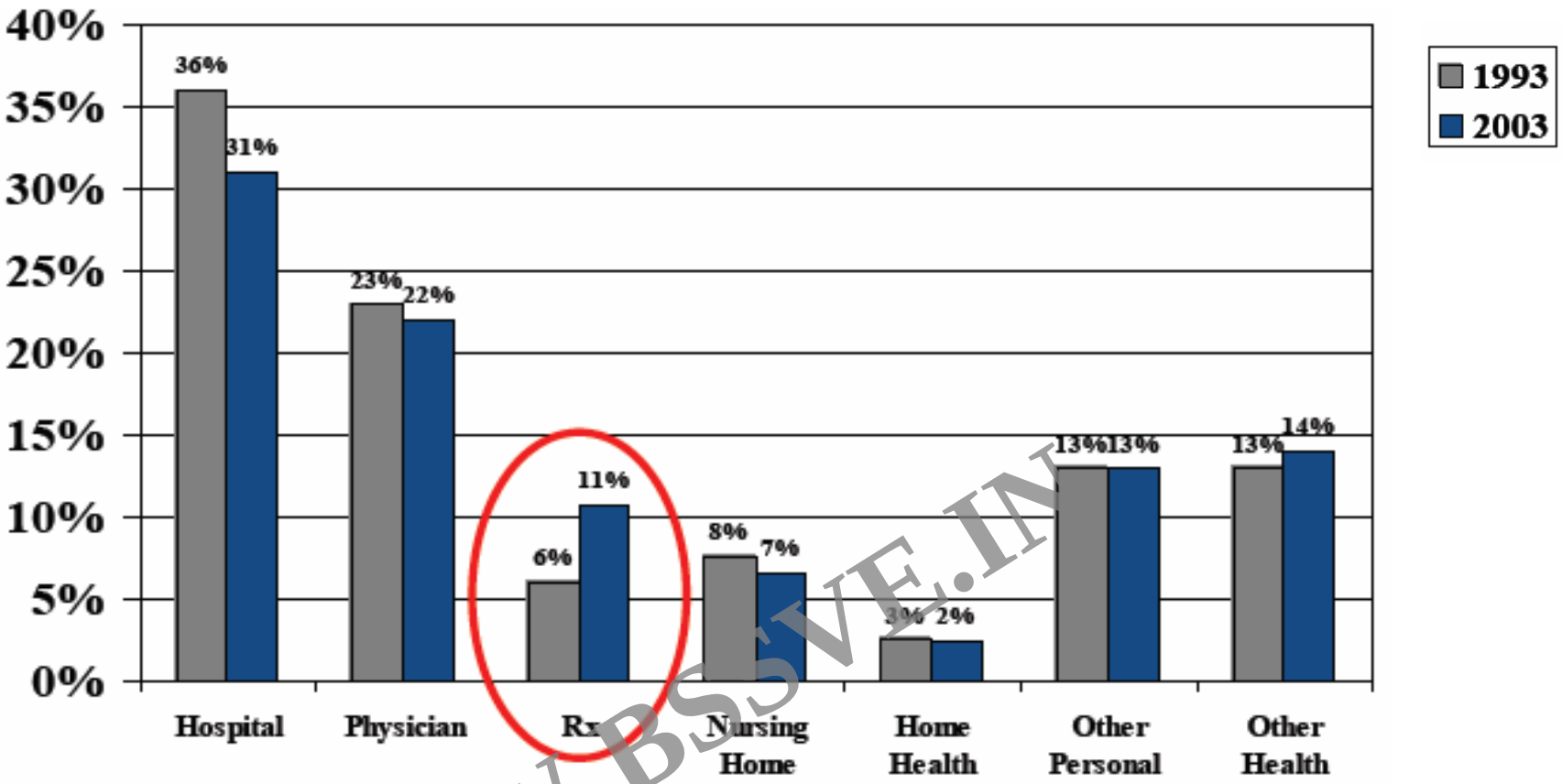
Source: IMS Health, Retail Drug Monitor Sept 2005 in US$ millions.
www.imshealth.com/vgn/images/portal/cit_40000873/53/63/76322469IMS%20Retail%20Drug%20Monitor%20September2005.pdf

Percent of All US Firms Offering Health Benefits:1996-2005



Adapted from Employer Health Benefits Survey 2005. Kaiser Family Foundation. http://www.kff.org/insurance/7315/sections/upload/7375.pdf.

OP Prescription Drugs as Percentage of US National Health Expenditures: 1993 v 2003



Adapted from: Smith C, et al. Health Spending Growth Slows in 2003. *Health Affairs* 2005;24(1):185-194. Exhibit 5.

Relative Contributions to Rising US Rx Expenditures: 1993-1997 vs 1997-2002

	1993-1997	1997-2002
Price	19%	25%
Rx Type	34%	34%
Utilization	47%	42%

Adapted from: Kaiser Family Foundation. Trends and Indicators, 2004 Update, Exhibit 1.17.

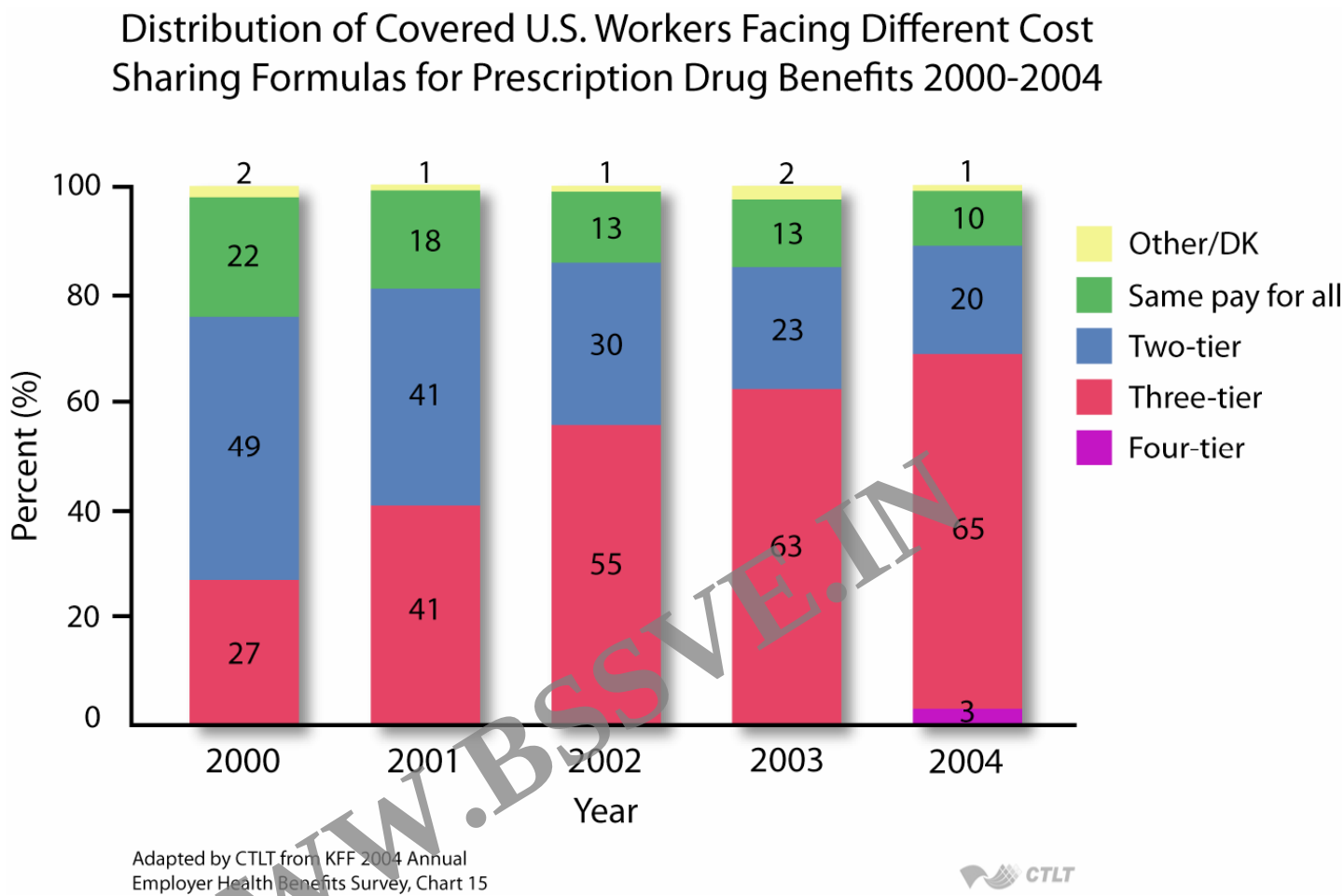
Access Barriers: Drugs Are Costly

- Major out-of-pocket expense
- Can represent as much as 20 percent of total national health expenditures, 60 percent of total recurrent health expenditures
- Drug expenditures are often second only to personnel salaries and benefits

Many Health Interventions Depend on Pharmaceuticals: Prevention & ACSCs

- Expanded Program on Immunization
- Integrated Management of Childhood Illness
- Directly Observed Treatment, Short-course
- Roll Back Malaria
- HIV prevention (social marketing of condoms)
- AIDS treatment and care

Coverage Distribution



US Non-compliance from Out-of-Pocket Costs*

			Out-Of-Pocket				Health Status	
Due to cost:	**Base: All Adults**	**Have Condition for Rx**	**$0-$100**	**$101-$250**	**$251-500**	**>$500**	**Excellent to Very Good**	**Fair to Poor**
Did not ask MD for an Rx	18%	23%	14%	37%	42%	42%	12%	33%
Did not fill an Rx	22%	30%	19%	50%	48%	44%	13%	41%
Used a lower dose to extend Rx	15%	21%	10%	35%	36%	41%	8%	29%
Used less than Rx'd	18%	25%	13%	45%	42%	46%	11%	37%

*Adapted from: Harris Interactive. Higher Out-of-Pocket Costs Cause Massive Non-Compliance in the Use of Prescription Drugs, and This Is Likely to Grow. Health Care News. 2002;2(22):2. http://www.harrisinteractive.com/

US Rx Compliance: Disease Specific Behaviors in the Past 12 Months

	Multiple Sclerosis	Hypertension	Depression
Not filled	15%	17%	30%
Delayed filling	24%	26%	41%
Taken in lower doses than prescribed	23%	14%	25%
Taken less often than prescribed	30%	29%	43%
Discontinued sooner than prescribed	15%	15%	30%

Adapted from: http://www.bcg.com/publications/files/TheHiddenEpidemic_Rpt_HCDec03.pdf

US Rx Compliance Behaviors & Gender:

How does female compliance affect household behaviors?

	Women	Men
Not filled	21%	15%
Delayed filling	30%	20%
Taken in lower doses than prescribed	15%	12%
Taken less often than prescribed	33%	26%
Discontinued sooner than prescribed	23%	18%

Adapted from: http://www.bcg.com/publications/files/TheHiddenEpidemic_Rpt_HCDec03.pdf

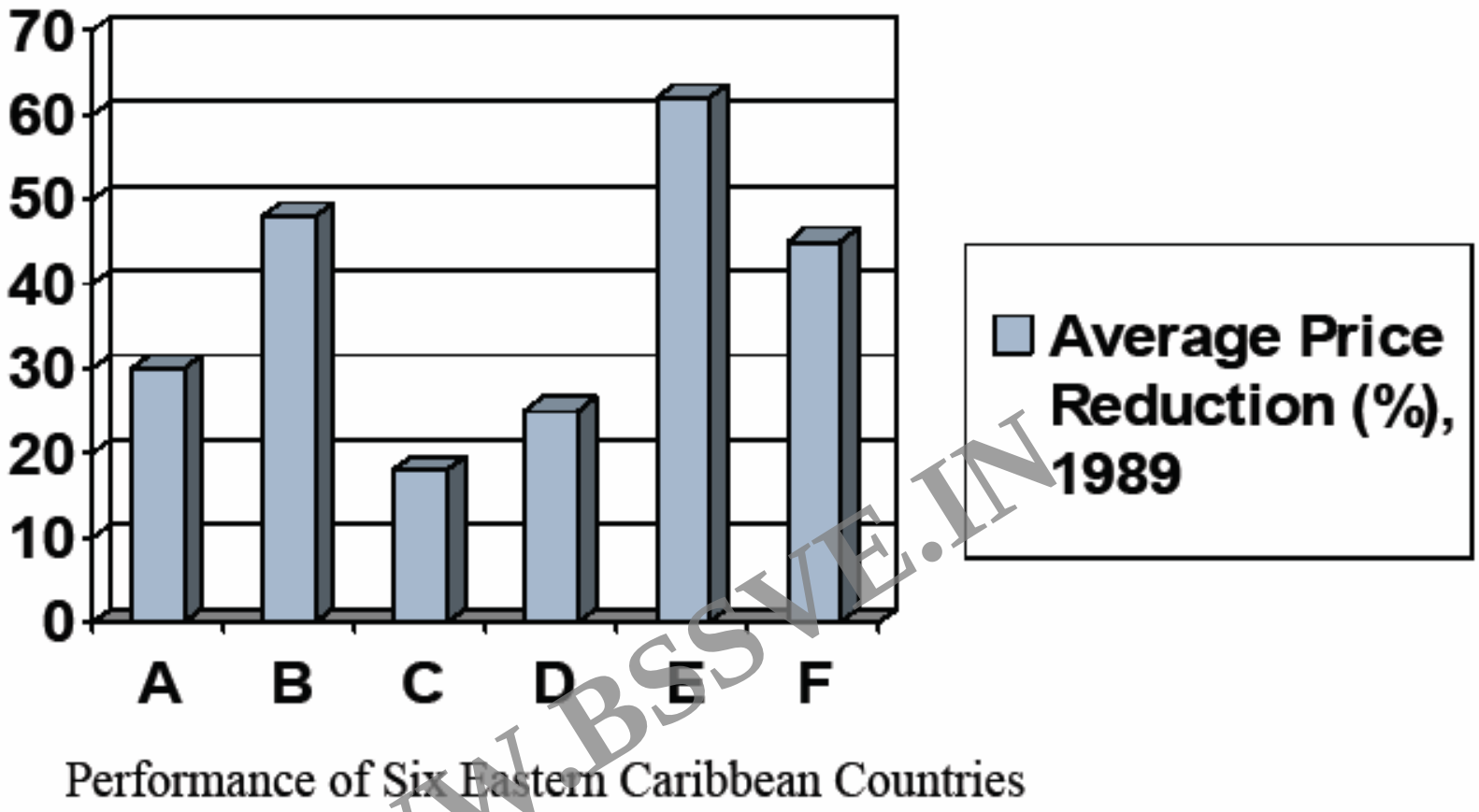
Drug coverage among Medicare beneficiaries with CHD/MI increases use of lifesaving drugs*

- Medicare beneficiaries with coronary heart disease
  - Statins recommended to lower cholesterol
  - Statins are costly
- 27.4 % with coverage used statins
- 4.1% without coverage used statins

What Is Known about Drug Management?

- Effective ambulatory Rx use can reduce morbidity and mortality
- Wise drug selection underlies all other improvements
- Effective management saves money and improves performance
- Rational drug use requires more than drug information
- Systematic assessment and monitoring are essential

Increased Efficiencies: Pooled Procurement



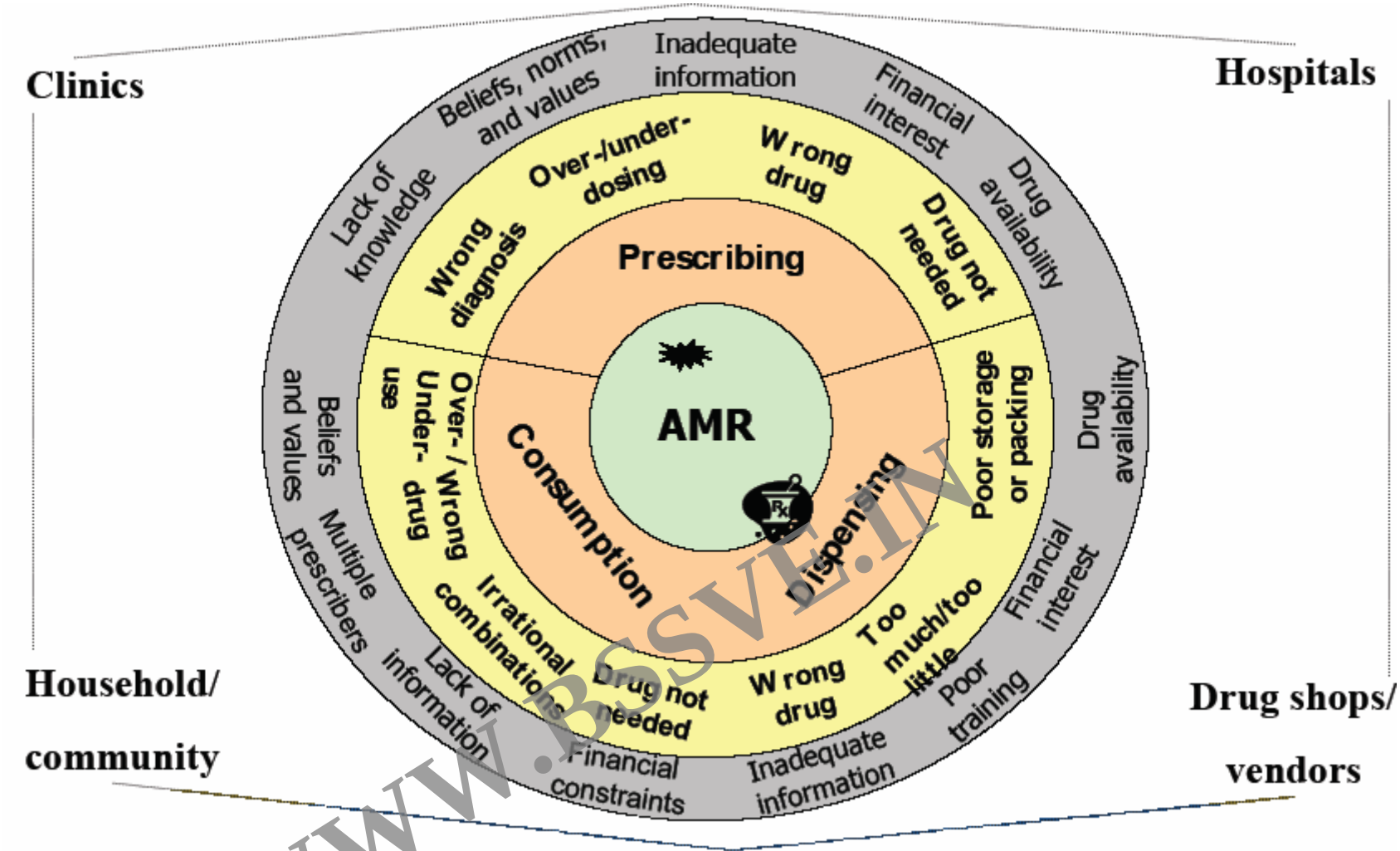
Performance of Six Eastern Caribbean Countries

Source: MSH: Management Sciences for Health. Used with permission.

Pharmaceutical Expenditures

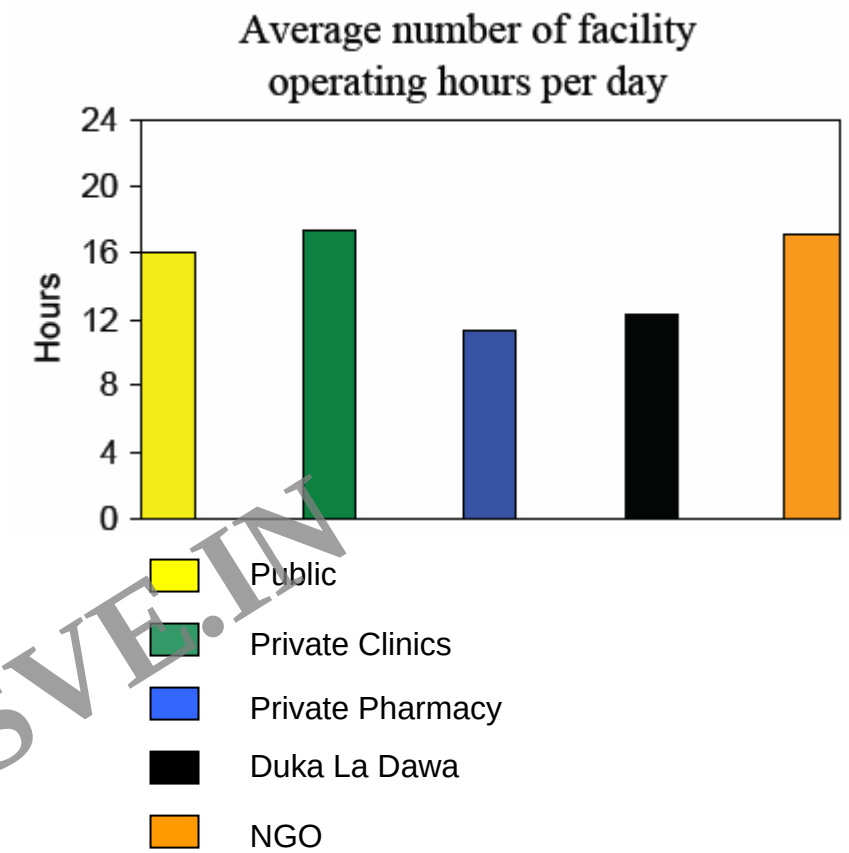
Region	Per Capita ($US/yr)	As % of GDP	Private Expenditures as % of Total
Africa	$8	0.86%	68%
Asia	$12	0.59%	76%
LA/C	$31	0.87%	75%
Developed Economies	$137	0.65%	33%

Understanding Medication Use



Source: MSH: Management Sciences for Health. Used with permission.

Geographic Accessibility: Tanzania



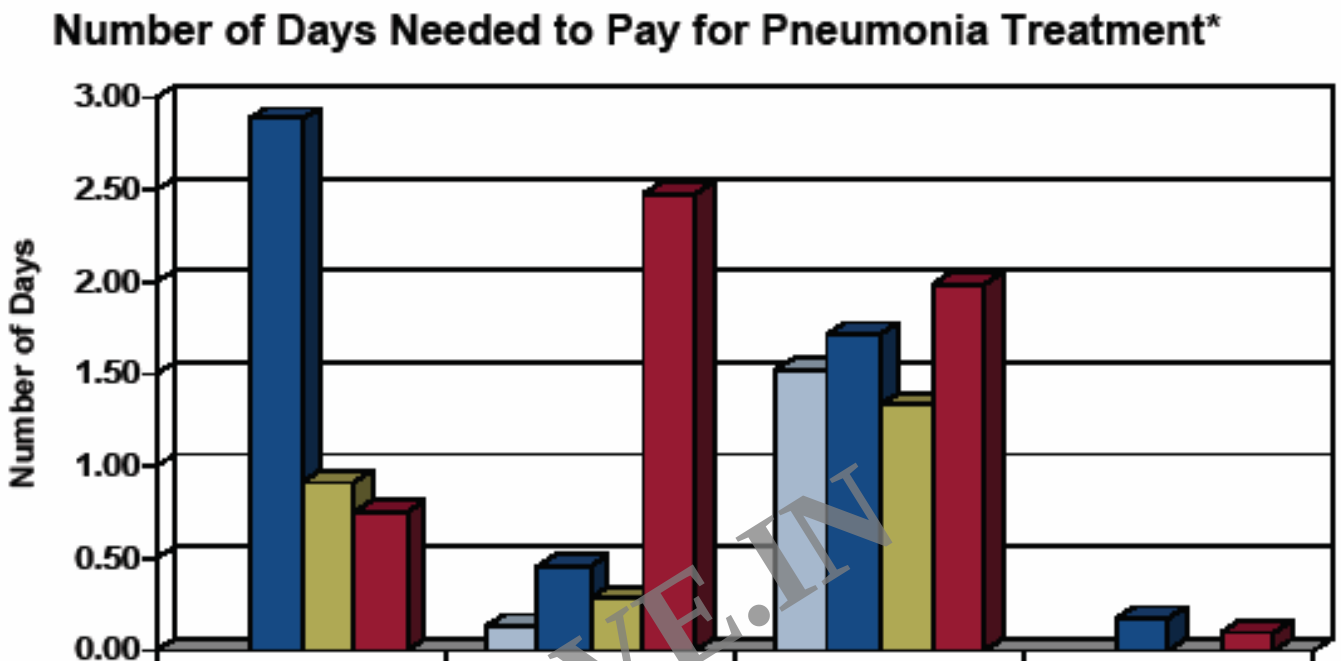
Distance to Health Facility

14% >10 km to public facility

6% >10 km to private drug retailer

Source: MSH: Management Sciences for Health. Used with permission.

Affordability: Cambodia, El Salvador, Ghana, India

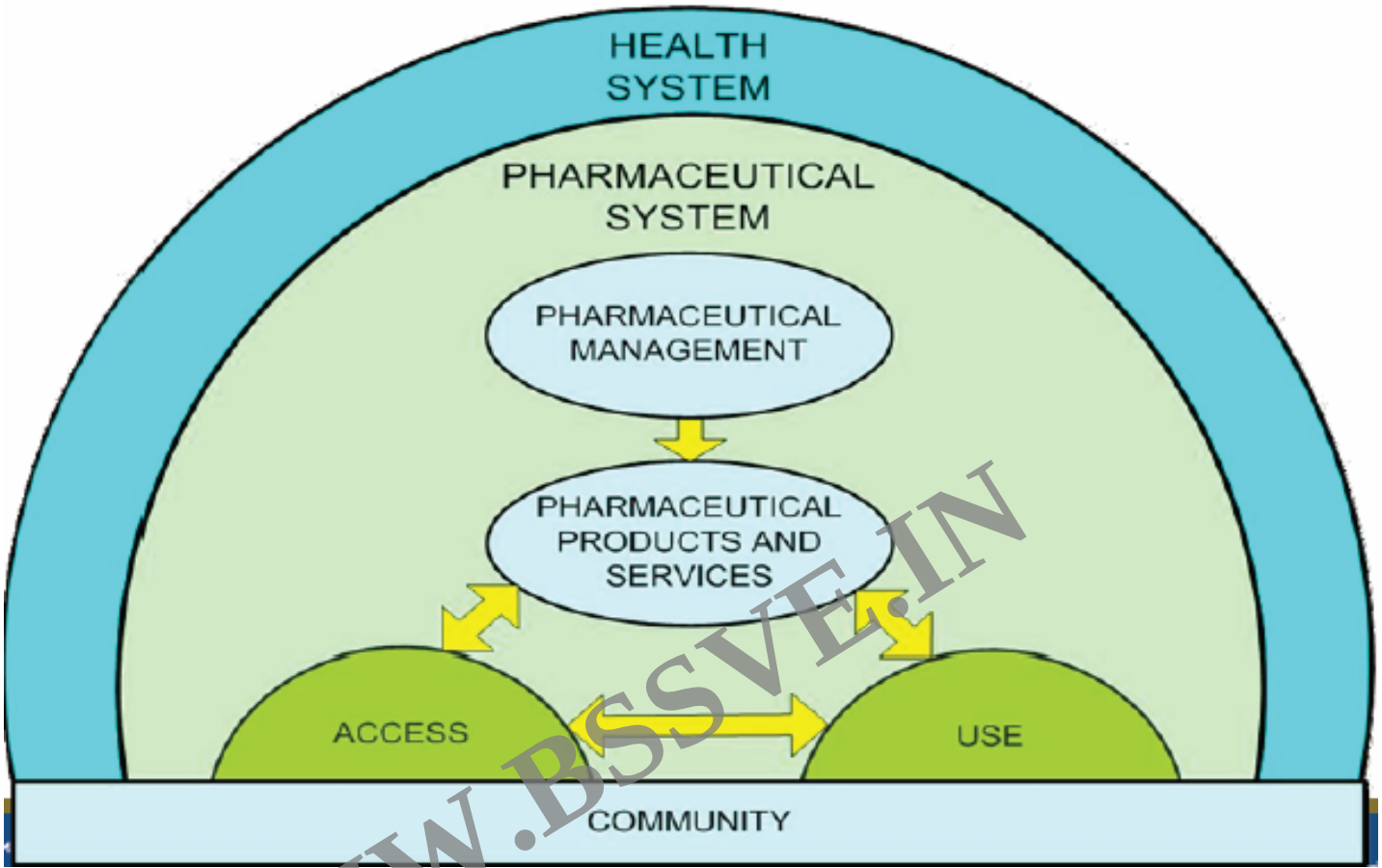


	Cambodia*	El Salvador*	Ghana**	India*
Public Facilities		0.13	1.52	
Private Facilities	2.89	0.45	1.72	0.17
NGO/Mission Facilities	0.91	0.28	1.33	
Private Pharmacies	0.75	2.48	1.99	0.09

*Child 1-5 years old, co-trimoxazole; **Adult, amoxicillin

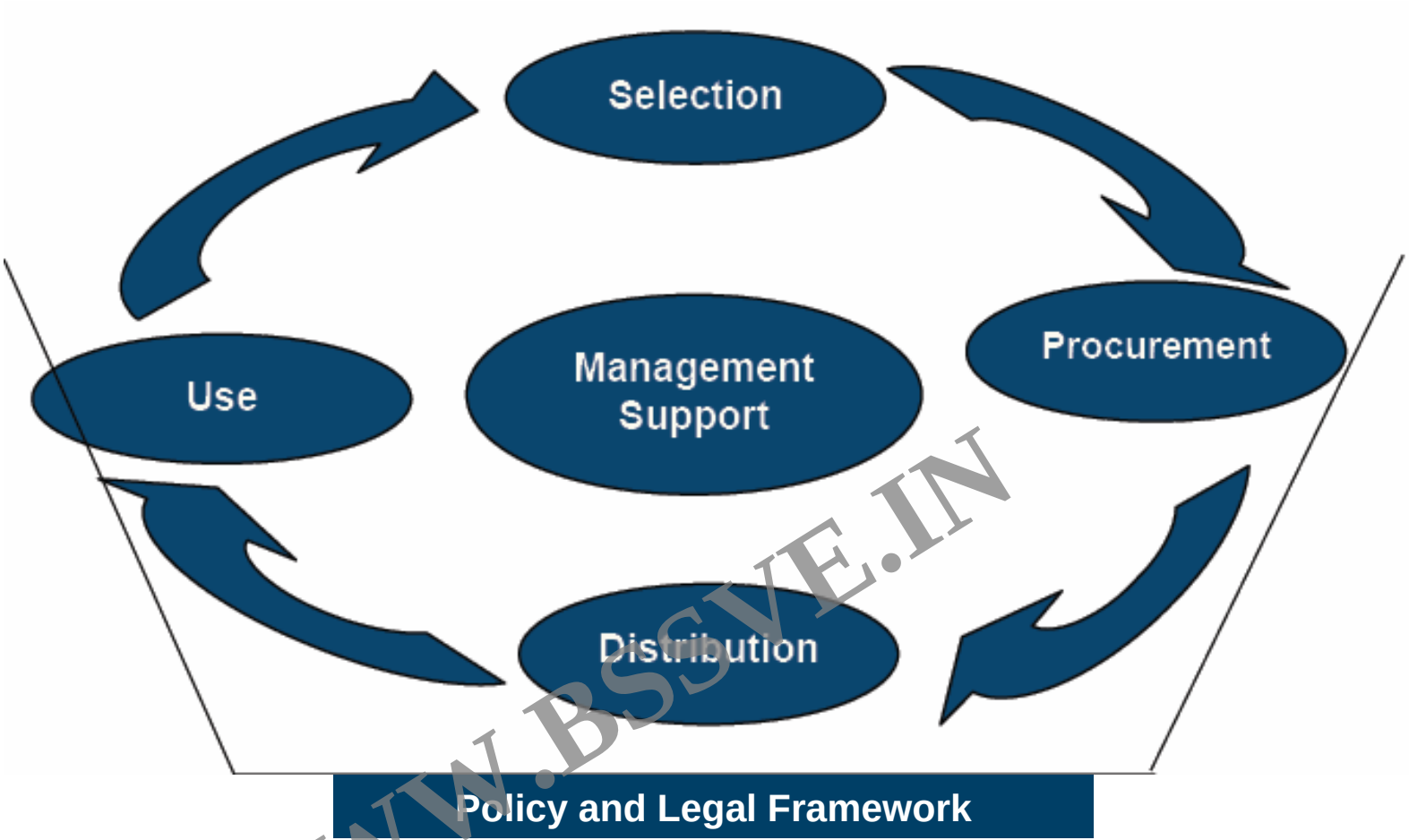
Source: MSH: Management Sciences for Health. Used with permission.

Pharmaceutical Management, Access, and Use of Medicines



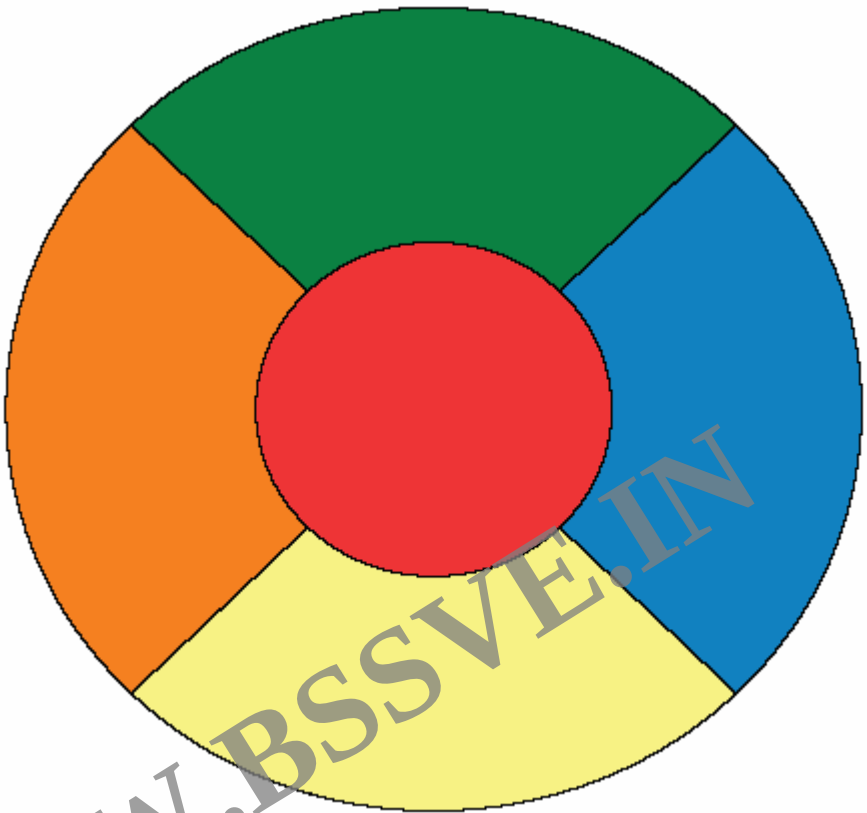
Source: MSH: Management Sciences for Health. Used with permission.

Pharmaceutical Management Cycle



Source: MSH: Management Sciences for Health. Used with permission.

Dimensions of Access & Potential Barriers

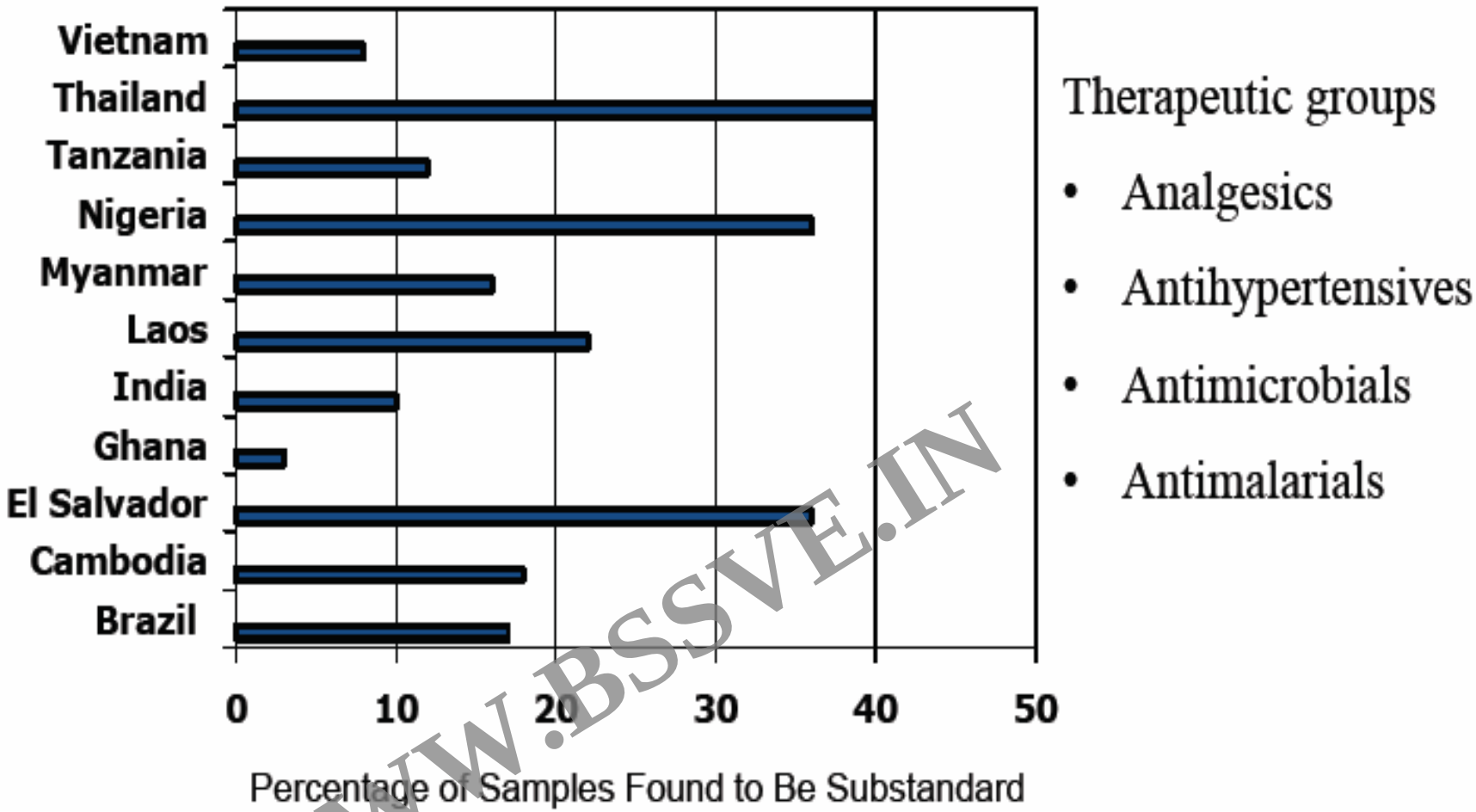


Essential Medicines Definition

Essential medicines are:

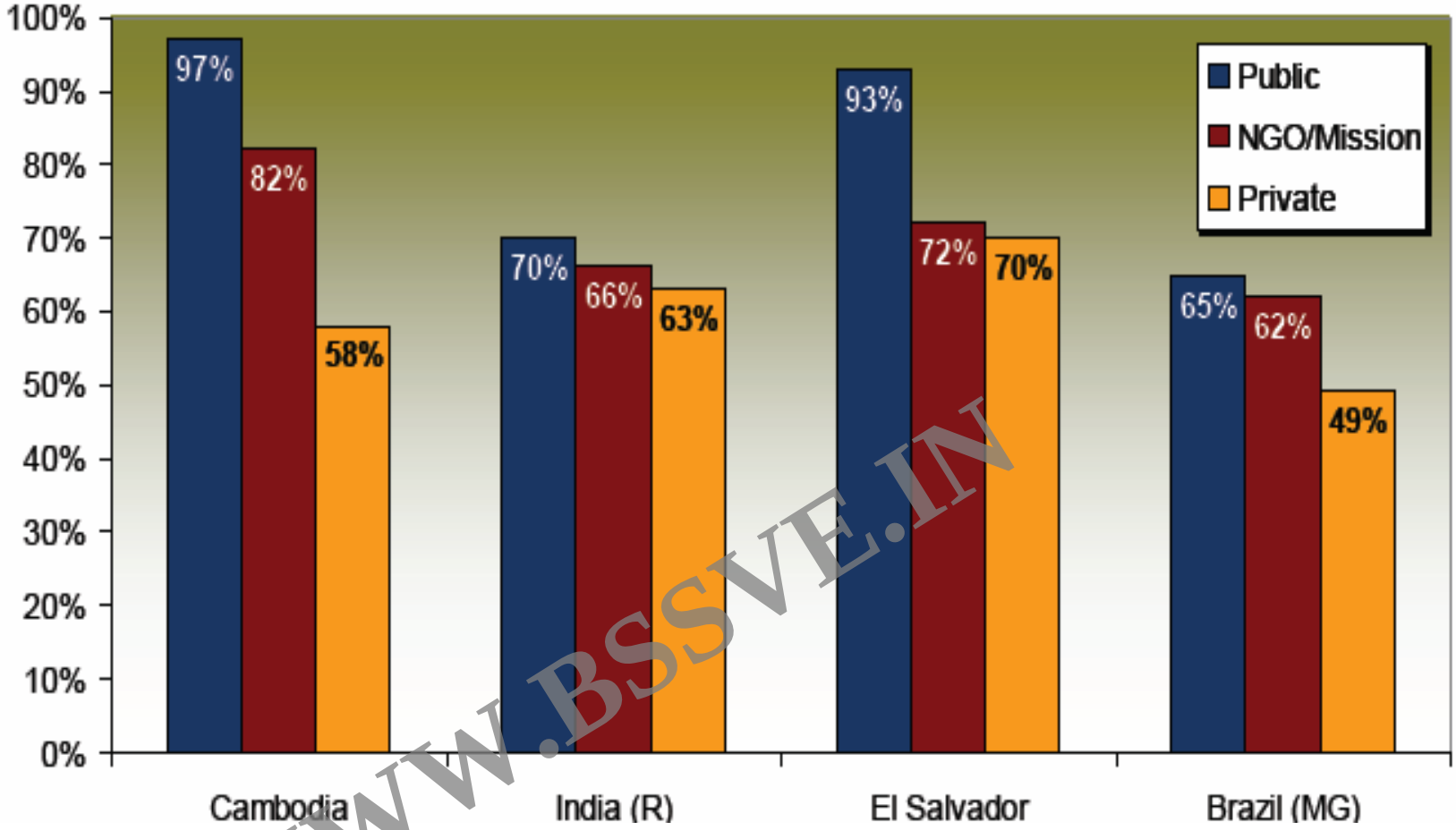
- those that satisfy the ***priority*** health care needs of the ***population***
- selected with due regard to ***public health relevance***, evidence on efficacy and safety, and ***comparative cost-effectiveness***
- intended to be available within the ***context of functioning health systems*** at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a cost that individuals and the community can ***afford***

Substandard Essential Medicines in Developing Countries



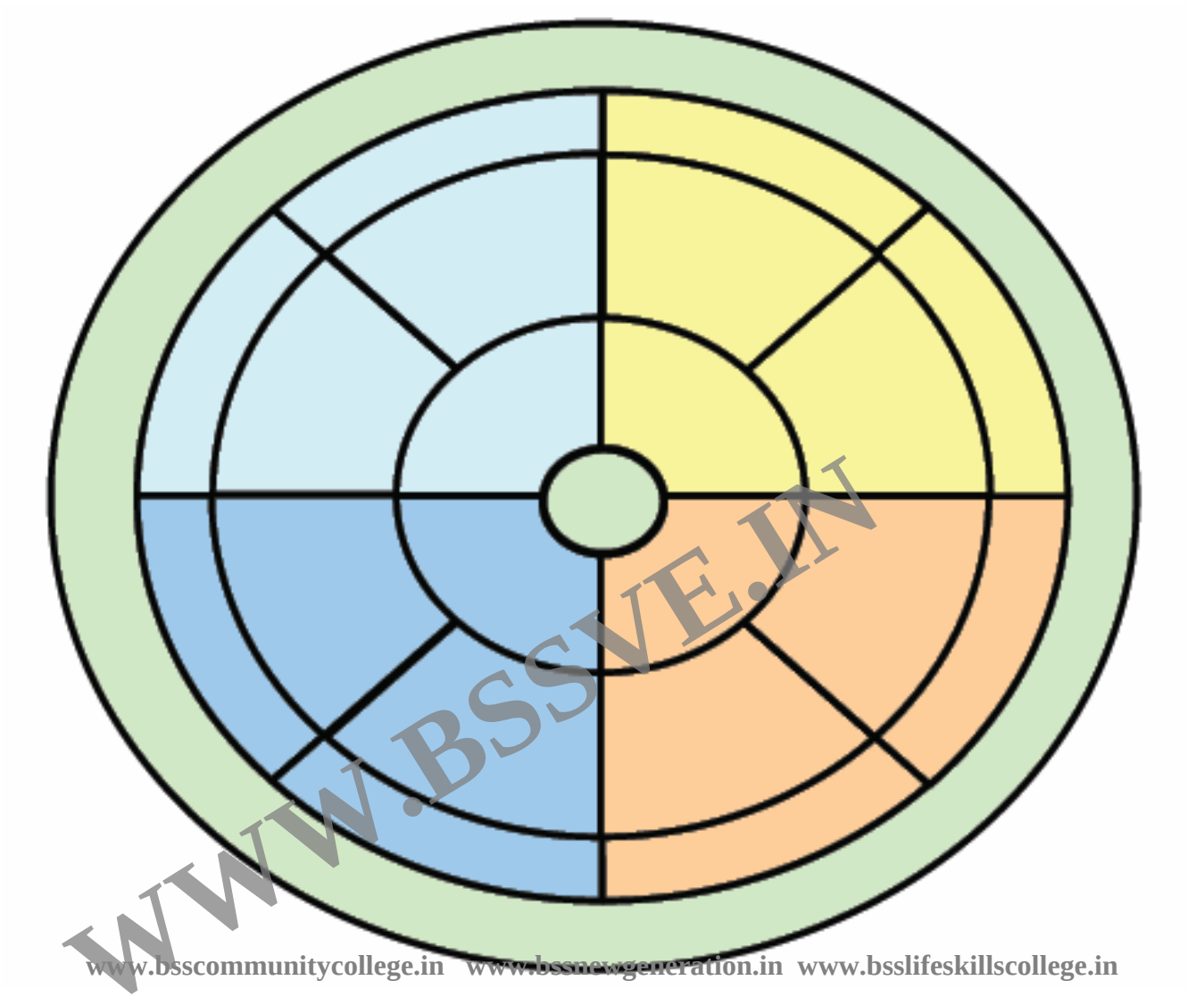
Source: MSH: Management Sciences for Health. Used with permission.

Percentage of Medicines Prescribed from Essential Medicines List, by Sector

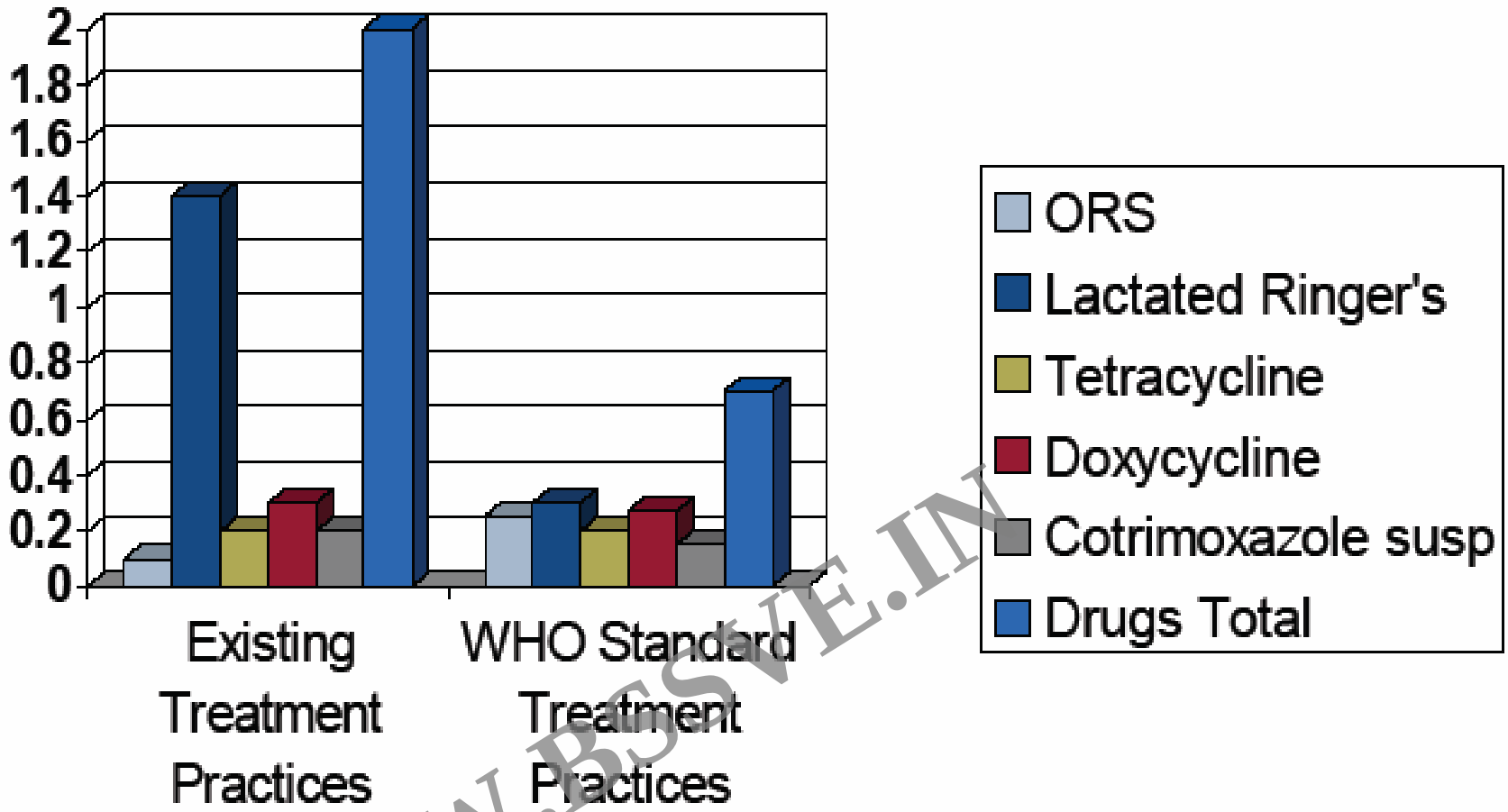


Source: MSH, Management Sciences for Health. Used with permission.

Understanding and Improving Access to Essential Medicines



Increased Efficiencies: STGs



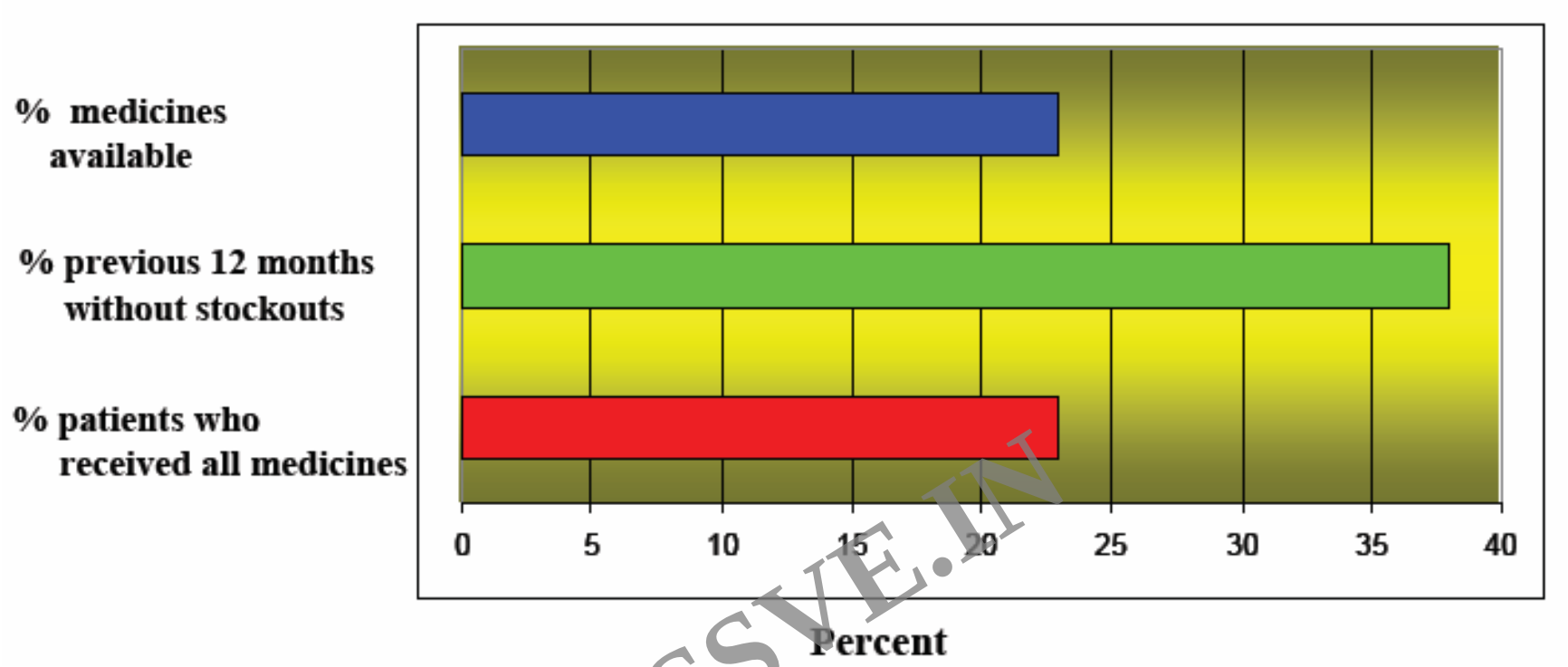
Total Annual drug costs in a Latin American country for treatments during a cholera epidemic, costs in millions of US$ (1991)

Source: MSH: Management Sciences for Health. Used with permission.

Challenges for Improved Public Drug Supply

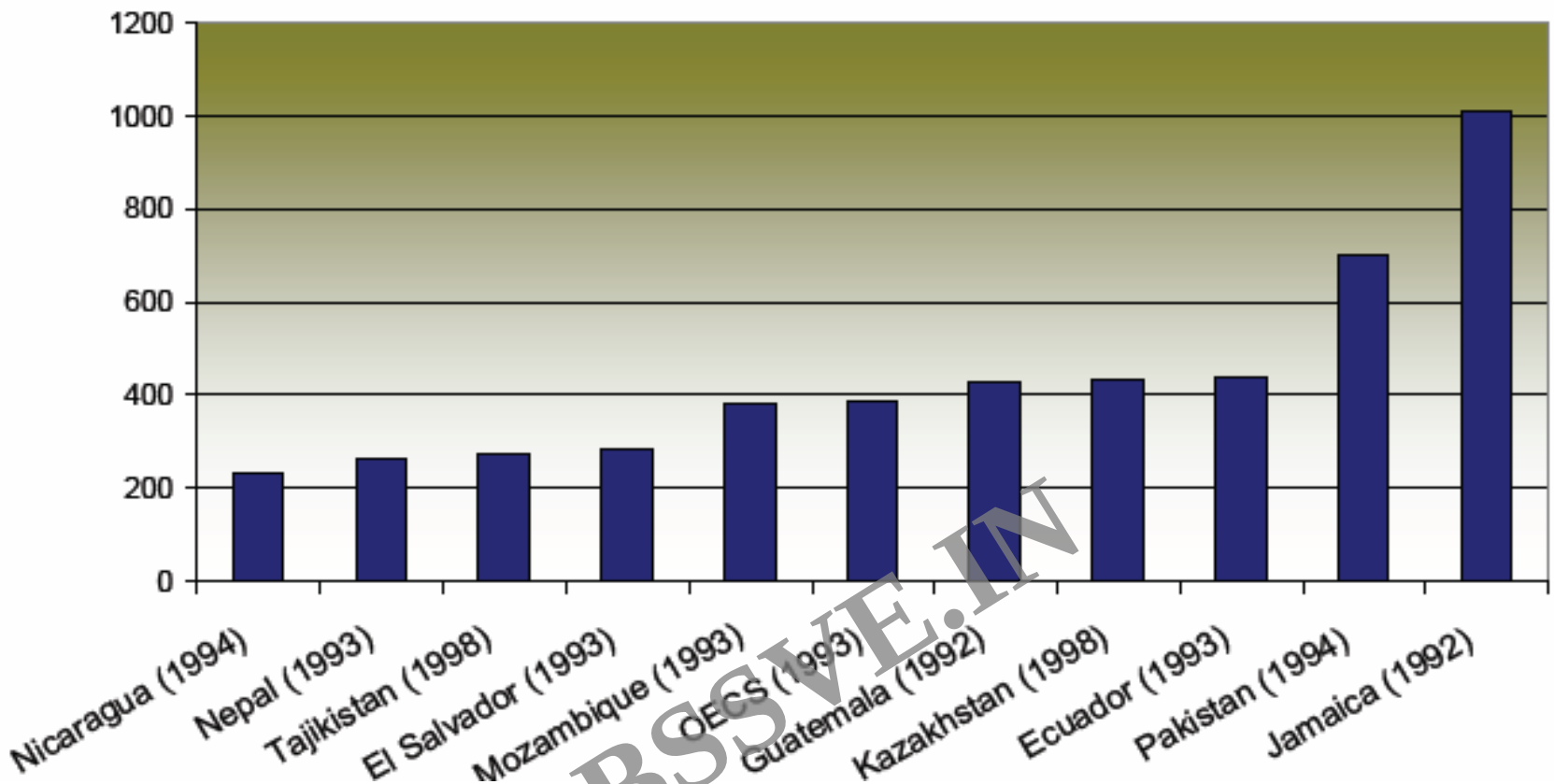
- Health reform, **equity**, and **financial sustainability**
- Efficiency
- Rational use
- Changing roles of public and private sectors

Essential Medicines
Availability & Dispensing in Dispensaries



Source: MSH: Management Sciences for Health. Used with permission.

Number of Medicines on National Essential Medicines Lists



Source: MSH: Management Sciences for Health. Used with permission.

Goals of a National Drug Policy

Health-Related

- Available essential drugs
- Improve attendance at health facilities
- Safe, affordable, and effective drugs
- Rational useProper selection of drugs
- Efficient supply

Economic

- Lower cost of drugs
- Reduce foreign exchange
- Provide jobs
- Improve efficiency and cost-effectiveness

Development

- Human resource development
- Improve infrastructure
- National production of drugs

Components of a National Drug Policy

- Legislative Framework
- Choice of Drugs
- Supply
- Rational Use of Drugs
- Economic Strategies for Drugs
- Human Resources Development
- Monitoring and Evaluation
- Research
- Technical Cooperation Among Countries

Session 6:

Enhancing Pharmaceutical Procurement

Michael Gabra

Session Objectives

- Recognize the characteristics of a good pharmaceutical procurement system
- Identify and describe the steps in the procurement cycle
- Discuss regional collaboration for procurement
- Discuss procurement of pharmaceuticals using USAID funds
- Discuss the challenges in the procurement of HIV/AIDS, TB, and malaria supplies

Session Outline

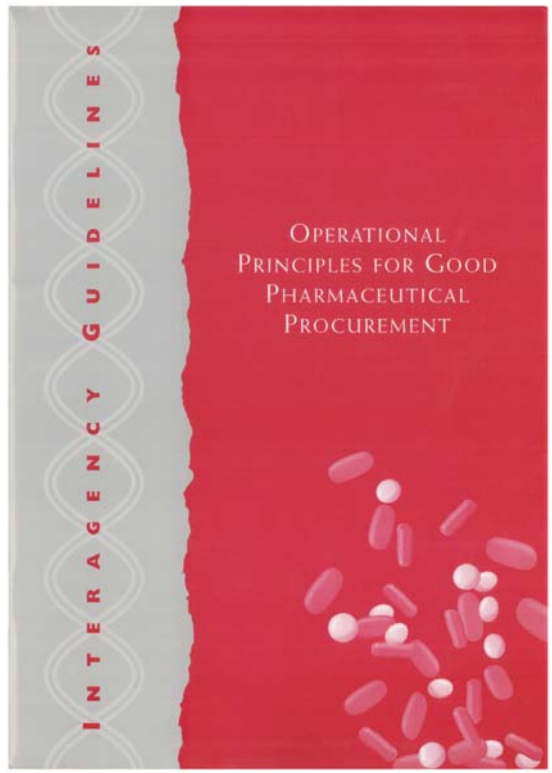
- Introduction
- Operational principles for good procurement
- The procurement cycle and methods
- Regional collaboration for procurement
- USAID procurement
- Procurement guidelines
- Challenges in procurement
- Case study

Objectives of a Good Procurement Program

- Procure the right drugs in the right quantities at the lowest possible total cost
- Select reliable suppliers of quality products
- Ensure timely delivery and notification

Operational Principles for Good Procurement

- Efficient and transparent management
- Drug selection and quantification
- Financing and competition
- Supplier selection and quality assurance



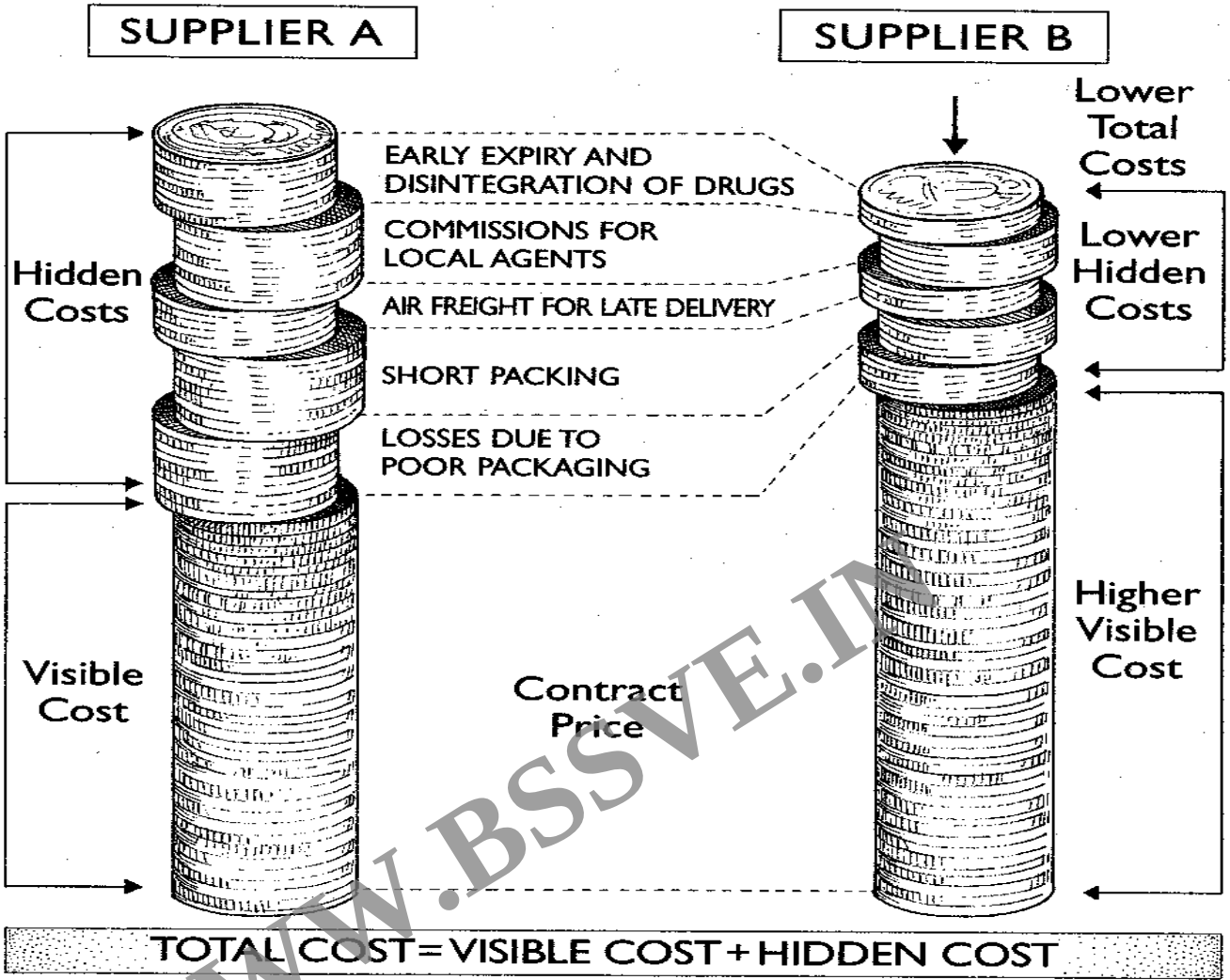
Good Procurement Practices (1)

- Generic name
- Limited to essential medicines list or formulary list
- Bulk purchases
- Formal supplier qualification and monitoring
- Competitive bidding process
- Commitment to a sole source

Good Procurement Practices (2)

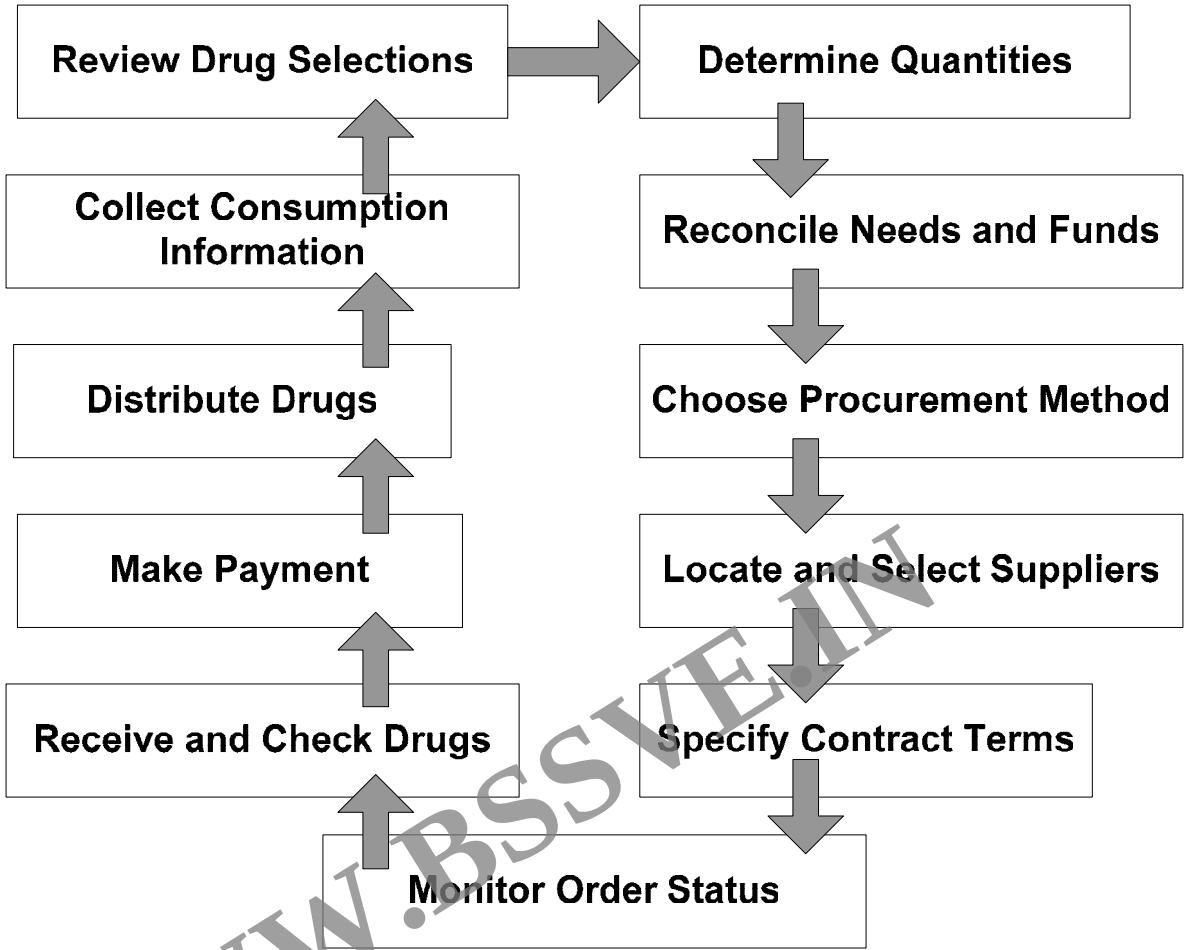
- Order quantities based on reliable estimate of actual need
- Reliable payment and good financial management
- Transparency and written procedures
- Separation of key functions
- Product quality assurance program
- Annual audit with published results
- Regular reporting on performance

Impact of Hidden Costs in Procurement



Source: MSH: Management Sciences for Health. Used with permission.

The Procurement Cycle



Source: MSH: Management Sciences for Health. Used with permission.

Procurement Methods

Method	Effect on Price	Lead Time	Work Load
Open Tender	Usually lowest prices	Moderate to long	High
Restricted Tender	Favorable	Moderate to long	High
Competitive Negotiation	Can be favorable	Short to moderate	Moderate
Direct Procurement	Usually highest prices	Short to moderate	Low

Defining Regional Collaboration for Procurement

- Wide variation exists in types of regional collaboration for procurement
- Spectrum of options ranges from the simple sharing of information to the actual pooling of resources and requirements combined with contracting and purchasing by an agency acting on behalf of the group of countries

Models of Regional/Country Collaboration

- Information Exchange
  - Informed buying
  - Coordinated informed buying
- Pooled Procurement
  - Group contracting
  - Central contracting

Characteristics of Models

Information Sharing		Pooled Procurement	
Informed Buying	**Coordinated Informed Buying**	**Group Contracting**	**Central Contracting**
Member countries share information about prices and suppliers	Member countries undertake joint market research, share supplier performance information, and monitor prices	Member countries jointly negotiate prices and select suppliers Member countries agree to purchase from selected suppliers	Member countries jointly conduct tenders and awards contracts through an organization acting on their behalf
Countries conduct procurement individually	Countries conduct procurement individually	Countries conduct purchasing individually	Central buying unit manages the purchase on behalf of countries

Pooled Procurement Initiatives

Name of Initiative	Year	No. of Countries	Status
FORMED	1986	3	Defunct
OECS/PPS	1986	9	Ongoing
Gulf Cooperation Council	1986	6	Ongoing
Arab Maghreb Union	1989	3	Inactive
ACAME	1996	6	?
Pacific Islands	1999	3	?

Advantages of Pooled Procurement

- Reducing drug costs through economies of scale
- Harmonizing drug registration among countries
- Harmonizing standard treatment guidelines (STGs) and essential medicines lists (EMLs)
- Improving quality assurance systems
- Improving supplier performance

Lessons Learned from Pooled Procurement

- Political will and organizational commitment
- Permanent and autonomous secretariat
- Harmonization and standardization
- Strong procurement systems
- Finances/reliable payment
- Quality assurance

USAID Procurement Requirements

- Pharmaceutical products
- Safety, efficacy, and quality
- “Buy America”
- Protection of U.S. patents

Challenges in Meeting USAID Procurement Requirements (1)

- Lack of guidance material to assist in what is perceived to be a complex process
- Preferential procurement of U.S. S/O, FDA-approved products may result in:
  - Increased costs and delays
  - Reduction in the impact of the program
  - Negative effect on the harmonization of pharmaceutical products within a country
  - The approved product may not be the most appropriate product for that program in the country context

Challenges in Meeting USAID Procurement Requirements (2)

Missing information

- Justification for not procuring a U.S. source of origin pharmaceutical product
- Information on the capacity of the program to use the product appropriately
- Data to attest to the safety, efficacy, and quality of the product

Options for Meeting Challenges

- Briefing document to provide guidance to cooperating agencies (CAs) and Missions on USAID procurement guidelines and procedures
- Technical assistance to USAID Missions and CAs in preparing requests for approval
- Implementation of Supply Chain Management System (SCMS)

World Bank Procurement Guidelines

- Principles
  - Need for economy and efficiency
  - Need to give all eligible bidders opportunity to compete
  - Encourage development of local industries in borrowing country
  - Importance of transparency

World Bank Procurement Methods

- International competitive bidding
- National competitive bidding
- Limited international bidding
- International or local shopping
- Direct procurement (sole sourcing)
- Cost-based selection
- Quality-based selection
- Limited budget selection

ARV Registration and Procurement – The Case of Ethiopia (1)

Background

- ART supported by GFATM and the U.S. President's Emergency Plan for AIDS Relief
- Distinct sites will receive ARV drug support from the Emergency Plan or GFATM
- First-line ARVs for adults have been introduced only for paying patients
- National treatment guidelines were under revision at the time of quantification and procurement
- Drug requirements for 6 months are to be received in two shipments

ARV Registration and Procurement – The Case of Ethiopia (2)

Registration

- Manufacturers are not interested in registering some drugs in Ethiopia
- Some manufacturing sites and pack sizes vary from those of registered products
- Full provision of second-line drugs has to be postponed until national treatment guidelines are endorsed

Quantification

- Uptake of newly introduced pediatric and second-line treatment unknown
- Intensive collaboration crucial for agreement on drug selection and projection of the capacity for scaling up

Pharmaceutical Donations

- Types
  - Solicited
  - Unsolicited
- Problems

Issues in Procurement of ATM Drugs and Supplies (1)

- Quantification of needs
- Chaotic and confused global market situation
- Doha Declaration on the TRIPS Agreement
- Donation programs
- Limited number of sources/suppliers
- High cost of supplies

Issues in Procurement of ATM Drugs and Supplies (2)

- Potential for corruption
- Varied and changing treatment regimens
- Variety of formulations
- Quality concerns
- Limited knowledge
- Limited sources of raw materials

Common Procurement Challenges

- Absence of a comprehensive procurement policy
- Inadequate rules, regulations, and structures
- Public sector staff with little experience and training to respond to market situations
- Government funding that is insufficient and/or released at irregular intervals
- Donor agencies with conflicting procurement regulations
- Fragmented drug procurement at provincial or district level
- Lack of unbiased market information
- Corruption and lack of transparency

Summary

- Characteristics of a good pharmaceutical procurement system
- Steps in the procurement cycle
- Regional collaboration for procurement
- USAID procurement procedures
- Challenges in the procurement of HIV/AIDS, TB, and malaria supplies

Session 3:

Drug Manufacture, Industrial Pharmacy Considerations, Quality Assurance, and Regulation

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Tom Layloff, Management Sciences for Health

Objectives

- Be familiar with drug manufacturing requirements and industry regulations
- Describe Good Manufacturing Practices (GMP)
- Understand requirements for developing domestic manufacturing capabilities
- Differentiate between brand vs generics and the conditions for interchange
- Become familiar with the procedures to prevent and detect counterfeit products
- Describe relevant drug regulations
- Describe the Guiding Principles for small national drug regulatory authorities
- Understand basics of and issues relating to drug product quality assurance
- Understand differences relating to full-scale manufacturing, small-scale institutional/local production, and extemporaneous compounding

The Drug Universe

- Begins with the Active Pharmaceutical Ingredient (API)
- APIs are chemicals have been shown through clinical studies to have desirable properties when used appropriately.
- APIs are extracts from natural products or chemically or biologically synthesized.
- The Safety and Efficacy (S&E) of APIs are established almost universally through the exquisite guidelines developed through the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), www.ich.org.
- The ICH guidelines are adopted into the laws and regulations of the ICH countries (European Union, Japan and United States) where essentially 100% of the drug research is conducted and which constitute over 85% of the world drug market.

ICH Quality Topics Checklist

Q1: Stability	Q1A(R): Stability Testing of New Drugs and Products (Revised)	Q1B: Photostability Testing	Q1C: Stability Testing for New Dosage Forms
	Q1D: Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products		
Q2: Analytical Validation	Q2A: Text on Validation of Analytical Procedures	Q2B: Methodology	
Q3: Impurities	Q3A(R): Impurities in New Drug Substances **(Revised)**	Q3B(R): Impurities in New Drug Products (**Revised)**	Q3C: Impurities: Residual Solvents
Q4: Pharmacopoeias	Q4: Pharmacopoeial Harmonisation		
Q5: Biotechnological Quality	**Q5A**: Viral Safety Evaluation	Q5B: Genetic Stability	Q5C: Stability of Products
	Q5D: Cell Substrates		
Q6: Specifications	Q6A: Chemical Substances with its Decision Trees	Q6B: Biotechnological Substances	
Q7: GMP	Q7A: GMP for Active Pharmaceutical Ingredients		

More on APIs

- Chemically synthesized APIs (Fine Chemicals) are produced primarily in the Chindia economic block, Korea and Italy (near Milan).
- Biotechnology derived APIs are almost all manufactured in the ICH regions
- The clinical studies—Phase III—define the therapeutic window—more drug may be toxic and less may be ineffective.
- Summary: Clinical studies are used to define the safety and efficacy of a drug product containing the API and the therapeutic window.

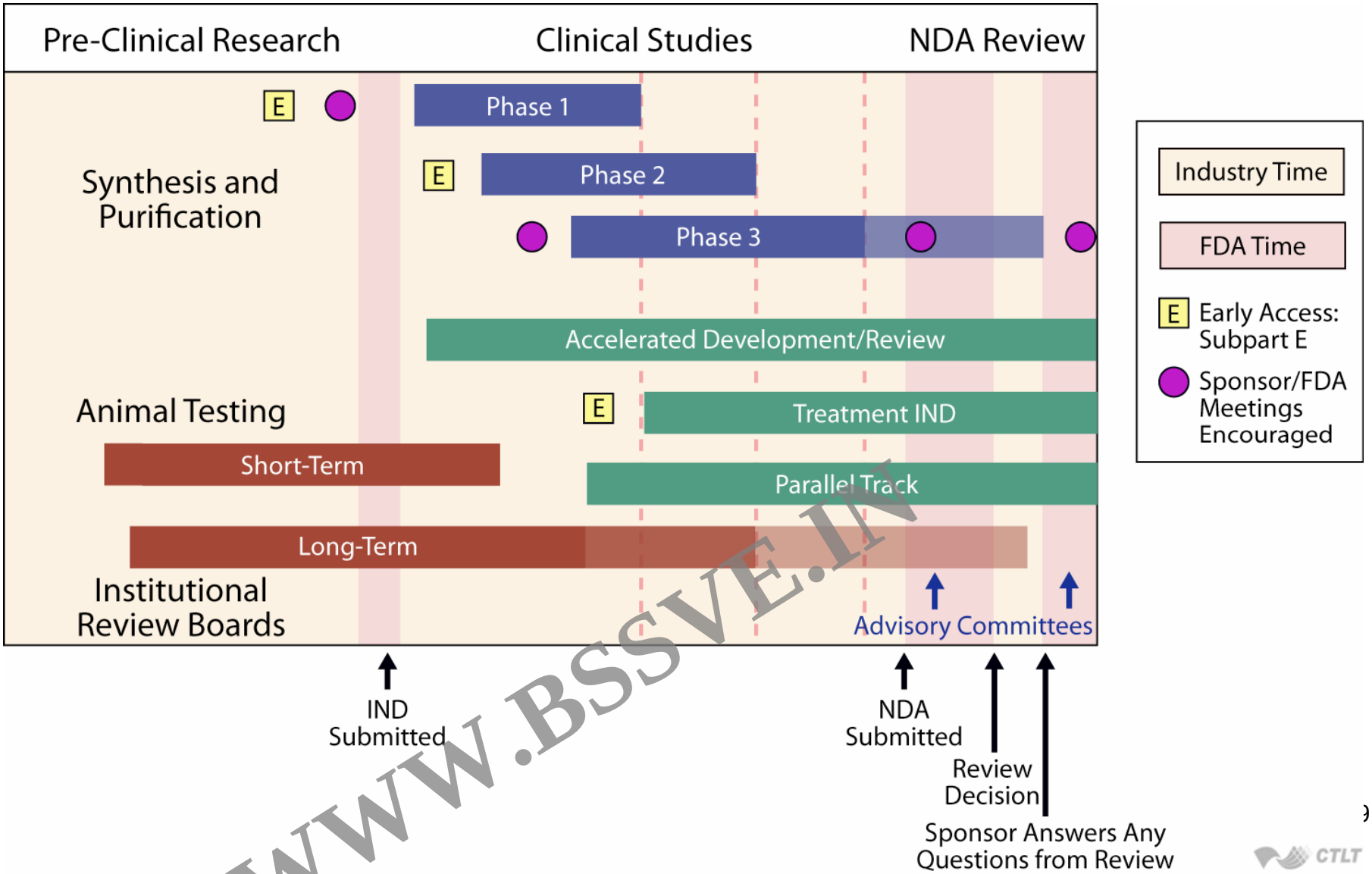
Drug Products

- Excipients used to formulate APIs into drug products are generally food grade chemicals—Bulk Commodities. Excipients are used to make the drug more convenient, palatable or effective
  - 325 mg Tylenol Excipients--cellulose, corn starch, magnesium stearate, sodium starch glycolate
- **Some Common Dosage Forms:** Capsules, Tablets, Chewable Tablets, Granules, Creams, Gels, Ointments, Injections, Powder for Injection, Oral Solutions, Suspensions, Syrups, Powder for Suspensions, Suppositories, Inhalers, Powder for Inhalation

New and Generic Drugs

- Generic drugs are off-patent products
- New and Generic Drugs frequently are give proprietary trade names for market leverage. Tylenol brand acetaminophen and Bayer brand aspirin are good examples of trade name off patent products. In Namibia I encountered at a pharmaceutical distributor 28 trade named amoxicillin products.
- The names of the API are assigned in the International Non-proprietary Names (INN) by WHO or in the United States Adopted Names (USAN) established by the AMA, USP and APhA.

New Drug Development



Drug Regulation

- Commerce Issues
  - When you purchase a 100 tablet bottle of 325 mg Aspirin do you get 100 tablets?
  - Does each Aspirin tablet contain 325 mg of Aspirin?
  - 325 mg is a pharmaceutical “term of art.”
    - Each tablet contains 85-125% and on the average they contain 90-110%.
    - Chemically 325 mg means 324.6-325.4 mg.
- Therapeutic Issues
  - Do the tablets disintegrate and release the drug for absorption?
  - Are there undesirable impurities present in the formulation?

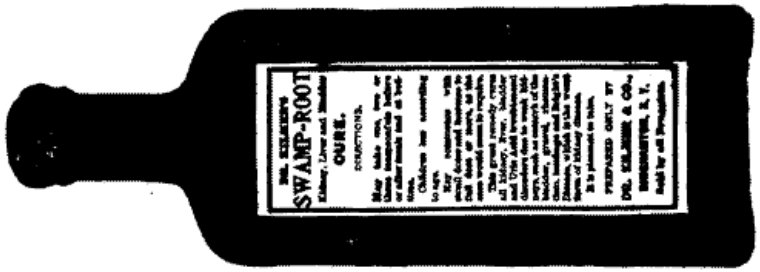
Commerce Issues

- Initially defined in pharmacopoeias which were established by practitioners to govern commerce in therapeutic “weeds and seeds.” The United States Pharmacopeia was established in 1820 by practitioners to govern their commerce.
- Pharmacopoeias contain monographs which define testing procedures and limits for assessing product quality.
- There are approximately 30 national pharmacopoeias from Argentina to Yugoslavia in addition to the African, European and International Pharmacopoeias.
- Identity, assay, dosage uniformity, API release from matrix, sterility, impurities, etc.
- Since the USP already was the basis for commerce in the US when the 1906 FDA legislation was enacted, it was cited for regulation and law enforcement of quality standards.
- The 1906 FDA legislation was a commerce law. It prohibits interstate commerce in misbranded and adulterated foods and drugs.

Cascara Sagrada is the dried bark of *Rhamnus purshiana* De Candolle (Fam. Rhamnaceae).

- Usually in flattened or transversely curved pieces, occasionally in quills of variable length and from 1 to 5 mm in thickness. The outer surface is brown, purplish brown, or brownish red, longitudinally ridged, with or without grayish or whitish lichen patches, sometimes with numerous lenticels and occasionally with moss attached. The inner surface is longitudinally striate, light yellow, weak reddish brown, or moderate yellowish brown. The fracture is short with projections of phloem fiber bundles in the inner bark.

CERTIFICATE OF PURITY



This is to Certify that Dr. Kilmer's Swamp-Root, the great kidney, liver and bladder remedy, is purely vegetable and does not contain any calomel, mercury, creosote, morphine, opium, strychnine, cocaine, nitrate potash (salt-petre), bromide potassium, narcotic alkaloid, whiskey, wine or any harmful or habit producing drugs. Swamp-Root was discovered through scientific research and study by Dr. Kilmer, who graduated with honors and is now actively engaged in the practice of his profession, which calling he has successfully followed many years. {State of New York, County of Broome, } S. S. City of Binghamton, }

Jonas M. Kilmer, senior member of the firm of Dr. Kilmer & Co., of the City of Binghamton, County of Broome, State of New York, being duly sworn, deposes and says that the guarantee of purity of Swamp-Root, as described in the foregoing certificate, is in all respects true.

Subscribed and sworn to before me April 26. 1898.

Jonas M. Kilmer

James O. Hasbrouck
Notary Public

Dr. Kilmer's Swamp-Root is not recommended for everything, but if you have kidney, liver or bladder trouble, it will be found just the remedy you need. Swamp-Root makes friends.

Each bottle contains the same standard of purity, strength and excellence.

You may have a sample bottle of Swamp-Root free by mail, if you have not already had one.

When writing to Dr. Kilmer & Co., Binghamton, N. Y., be sure to mention reading this generous offer in this paper.

If you are already convinced that Swamp-Root is what you need, you can purchase the regular fifty-cent and one-dollar size bottles at drug stores everywhere. Don't make any mistake, but remember the name, Swamp-Root, Dr. Kilmer's Swamp-Root, and the address, Binghamton, N. Y. on every bottle.

US FDA Legal Tipping Points

- **1938** Safety legislation enacted following the elixir sulfanilamide fiasco. Sulfanilamide was dissolved in ethylene glycol to prepare a toxic elixir. Drug products introduced into commerce after 1938 had to be shown to be safe. Products marketed prior to 1938 were grandfathered and the onus was on FDA to demonstrate lack of safety for action. Relived again by accident in Haiti with the acetaminophen elixir prepared with impure glycerol.
- **1941** Nearly 300 deaths and injuries result from distribution of sulfathiazole tablets tainted with phenobarbital. The incident prompts FDA to revise manufacturing and quality controls drastically, the beginning of what would later be called good manufacturing practices (GMPs).
- **1962** Efficacy legislation enacted following the thalidomide disaster. Drug products introduced into commerce after 1962 had to be shown to be effective for intended use. Drug products in commerce before 1962 were reviewed for efficacy. Panels of experts were established by the National Academy of Sciences-National Research Council to conduct the Drug Efficacy Study Implementation (DESI).

A Generic Drug Is

- A generic drug is a drug that is bioequivalent to an innovator drug with respect to pharmacokinetic and pharmacodynamic properties.
- Generic drugs must contain the same active ingredient at the same strength as the innovator brand, be bioequivalent, and are required to meet the same pharmacopeial standards as applicable.
- Generic drugs are identical in dose, strength, route of administration, safety, efficacy, and intended use.

Hatch-Waxman Amendments to FFD&C Act

- **1984** Legislation enacted to require FDA to approve applications to market generic versions of brand-name drugs after expiration of patents and exclusivities without repeating the research done to prove them safe and effective thereby avoiding expensive pre-clinical and clinical trials. Abbreviated New Drug Applications (ANDA).
- **1992** Generic Drug Enforcement Act imposes debarment and other penalties for illegal acts involving ANDA.
- Bolar Pharmaceutical Company, pleaded guilty in 1991 to charges that it submitted false test results to win Federal approval for some generic drugs.

New vs. Generic Review Processes

New Drug (ICH) Requirements	Generic Drug Requirements
1. Chemistry	1. Chemistry
2. Manufacturing	2. Manufacturing
3. Controls	3. Controls
4. Labeling	4. Labeling
5. Testing	5. Testing
6. Animal studies	
7. Clinical studies	6. Bioequivalence
8. Bioavailability	

1990s Generic Drug Fall-Out

- Circa is a cleaned-up reincarnation of Bolar Pharmaceuticals, a generic drug maker whose chairman went to jail after the company was caught faking a test for the Food and Drug Administration. And Pharmaceutical Resources is the renamed Par Pharmaceuticals; officers of Par were convicted of bribing F.D.A. regulators.
- FDA Manager Charles Chang, admitted receiving about $15,000 worth of gifts, including furniture, computer equipment and an expense-paid trip to Hong Kong, to help speed applications for generic drugs through the approval process.
- Vitarine officials admitted that the data showing equivalence actually came from tests on the brand-named drug, not the generic.

Preparing an API for Patient Use

- To serve the patient's needs the API must be provided in the right amount in an appropriate vehicle.
- Compounding: Good Compounding Practices. In the US the practice of medicine and pharmacy is governed by state boards.
- "Production"
- Manufacturing: Current Good Manufacturing Practices. In the US API and drug product manufacturing are governed by the US FDA.

Compounding

Compounding involves the preparation, mixing, assembling, packaging, and labeling of a drug or device in accordance with a licensed practitioner's prescription under an initiative based on the practitioner/patient/pharmacist/compounder relationship in the course of professional practice. Compounding includes the following:

a. Preparation of drugs or devices in anticipation of prescription drug orders based on routine, regularly observed prescribing patterns.

b. Reconstitution of commercial products that may require the addition of two or more ingredients as a result of a licensed practitioner's prescription drug order.

c. Manipulation of commercial products that may require the addition of one or more ingredients as a result of a licensed practitioner's prescription drug order.

d. Preparation of drugs or devices for the purposes of, or as an incident to, research, teaching, or chemical analysis.

USP Compounding Practices

< USP >	Abbreviated Title
795	Nonsterile Compounding
797	Sterile Compounding
1075	Good Compounding Practices
1150	Pharmaceutical Stability
1160	Compounding Calculations
1191	Dispensing Stability

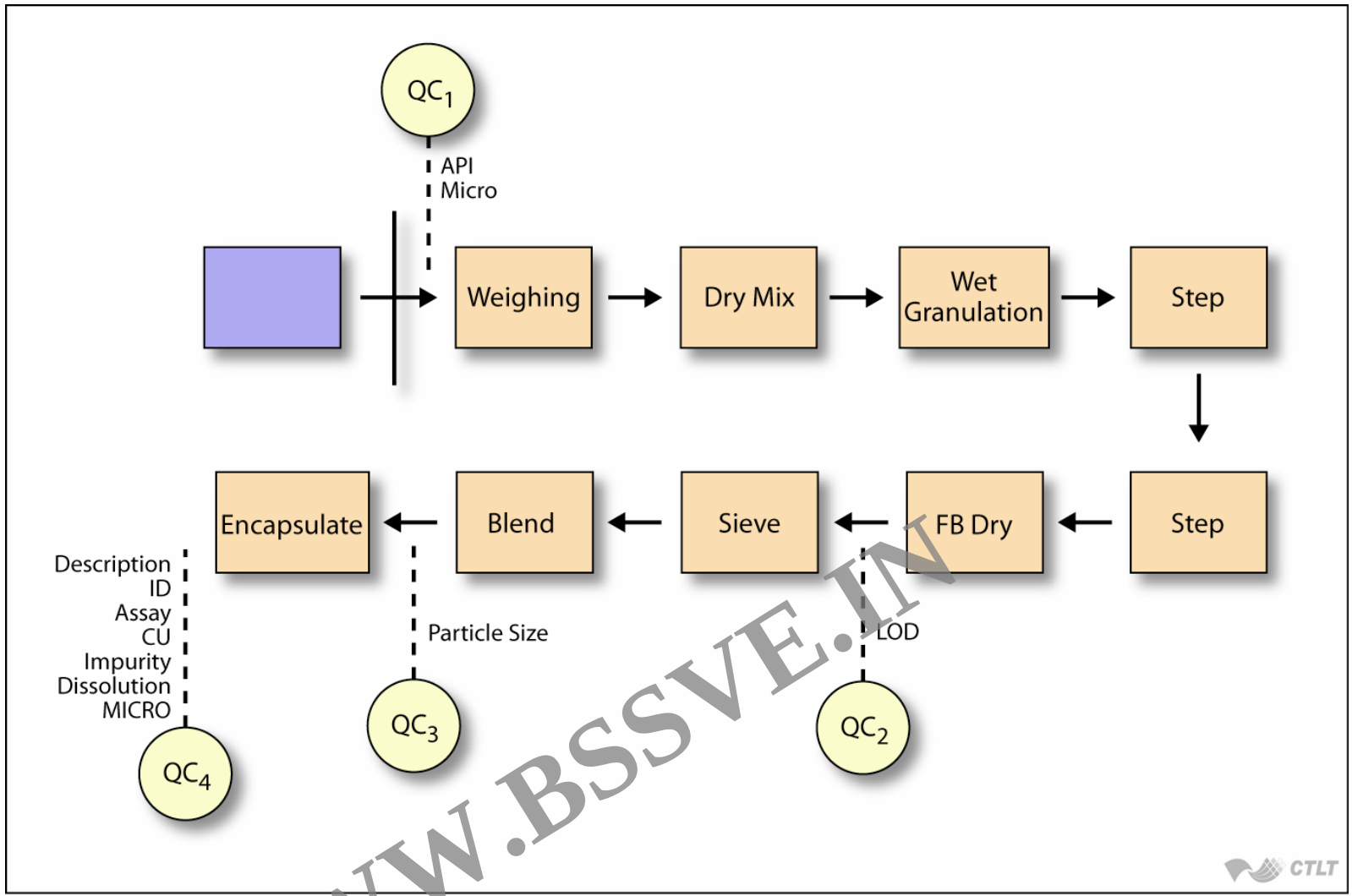
Manufacturing

- Manufacturing involves the production, propagation, conversion, or processing of a drug or device, either directly or indirectly, by extraction of the drug from substances of natural origin or by means of chemical or biological synthesis.
- Manufacturing also includes
  1. any packaging or repackaging of the substance(s) or labeling or relabeling of containers for the promotion and marketing of such drugs or devices;
  2. any preparation of a drug or device that is given or sold for resale by pharmacies, practitioners, or other persons;
  3. the distribution of inordinate amounts of compounded preparations or the copying of commercially available drug products; and
  4. the preparation of any quantity of a drug product without a licensed prescriber/patient/licensed pharmacist/compounder relationship.

Drug Manufacturing

- Mechanized Formulation
- API and Excipients are Blended and Processed into Products.
- Generally in Drug Manufacturing no chemical reactions are conducted.

A Manufacturing Process



Adapted by CTLT from GK Raju - MIT

Granulation and Milling

- Granulation end-point
- Flow characteristics, bulk density etc
- Homogeneity of granule
- Moisture content
- Particle size

Good Manufacturing Practices (GMP)

- GMPs are intended to assure the production of a uniform, consistent product. The WHO and US have published the flagship guidance. The manufacturing processes must be well-defined, documented and in demonstrated control.
- The GMP start with the quarantine of all received goods which after verification are released to production.
- The GMP end with the review of the finished product to assure that it complies with the stated requirements.
- It is estimated that the cost of quality manufacture costs 25-35% of sales.

Part 211 – Selected CGMP For Finished Pharmaceuticals

Subpart A - General Provisions

Subpart B - Organization and Personnel

211.22 Responsibilities of quality control unit.

211.25 Personnel Qualifications.

211.28 Personnel responsibilities.

Subpart C - Buildings and Facilities

211.46 Ventilation, air filtration, air heating and cooling.

211.58 Maintenance

Subpart D - Equipment

211.63 Equipment design, size, and location.

211.65 Equipment construction.

211.67 Equipment cleaning and maintenance.

211.68 Automatic, mechanical, and electronic equipment.

211.72 Filters.

Subpart E - Control of Components and Drug Product Containers and Closures

211.80 General requirements.

211.82 Receipt and storage of untested components, drug product containers, and closures.

211.84 Testing and approval or rejection of components, drug product containers, and closures.

211.86 Use of approved components, drug product containers, and closures.

Subpart F - Production and Process Controls

211.100 Written procedures; deviations.

211.101 Charge-in of components.

211.103 Calculation of yield.

211.105 Equipment identification.

211.110 Sampling and testing of in-process materials and drug products.

211.111 Time limitations on production.

211.113 Control of microbiological contamination.

211.115 Reprocessing.

Selected 211 CGMP Continues

Subpart G - Packaging and Labeling Control

211.122 Materials examination and usage criteria.

211.125 Labeling issuance.

211.130 Packaging and labeling operations.

211.134 Drug product inspection.

211.137 Expiration dating.

Subpart H - Holding and Distribution

211.142 Warehousing procedures.

211.150 Distribution procedures.

Subpart I - Laboratory Controls

211.165 Testing and release for distribution.

211.166 Stability testing.

211.173 Laboratory animals.

- **Subpart J - Records and Reports**
- 211.182 Equipment cleaning and use log.
- 211.184 Component, drug product container, closure, and labeling records.
- 211.186 Master production and control records.
- 211.194 Laboratory records.
- 211.198 Complaint files.
- **Subpart K - Returned and Salvaged Drug Products**

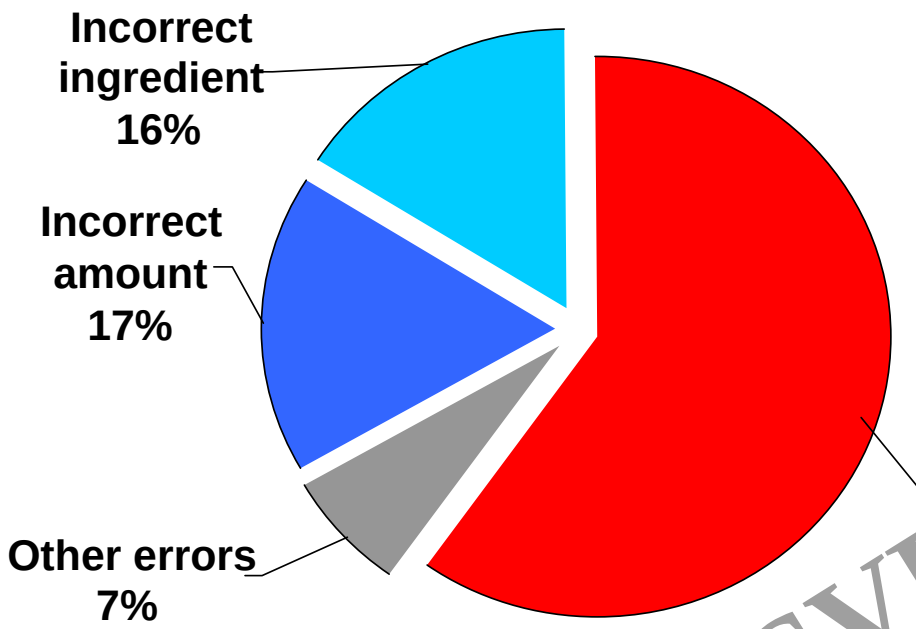
In Country Pharmaceutical Formulation Capacity

- Can GMP Formulation Plants Be Established in the Developing Countries??
- Can You Build Quality Toyota Vehicles In The US??
- Of Course
  - Fourth-largest automaker in America
  - 12 manufacturing plants in North America -- two additional facilities in the future
  - In 2004 at its North American facilities produced
    - > 1.44 million vehicles,
    - > 1.27 million engines and
    - nearly 390,000 automatic transmissions
- Ford Eliminating Up to 30,000 Jobs and 14 Factories
- Commercial viability is crucial for sustainability!!

Reasons for Poor Quality Pharmaceuticals

- Gaps in regulatory capacity: improper requirements and no capacity for implementation of requirements
- Global standards for generics: WHO has a comprehensive set of guidelines, but implementation varies
- Different quality requirements for export: very few countries effectively control quality of pharmaceuticals for export; certificates for export are issued more easily than are certificates for domestic markets
- Financial incentives: local manufacturers do not have sufficient incentives to meet international standards
- No enforcement actions.

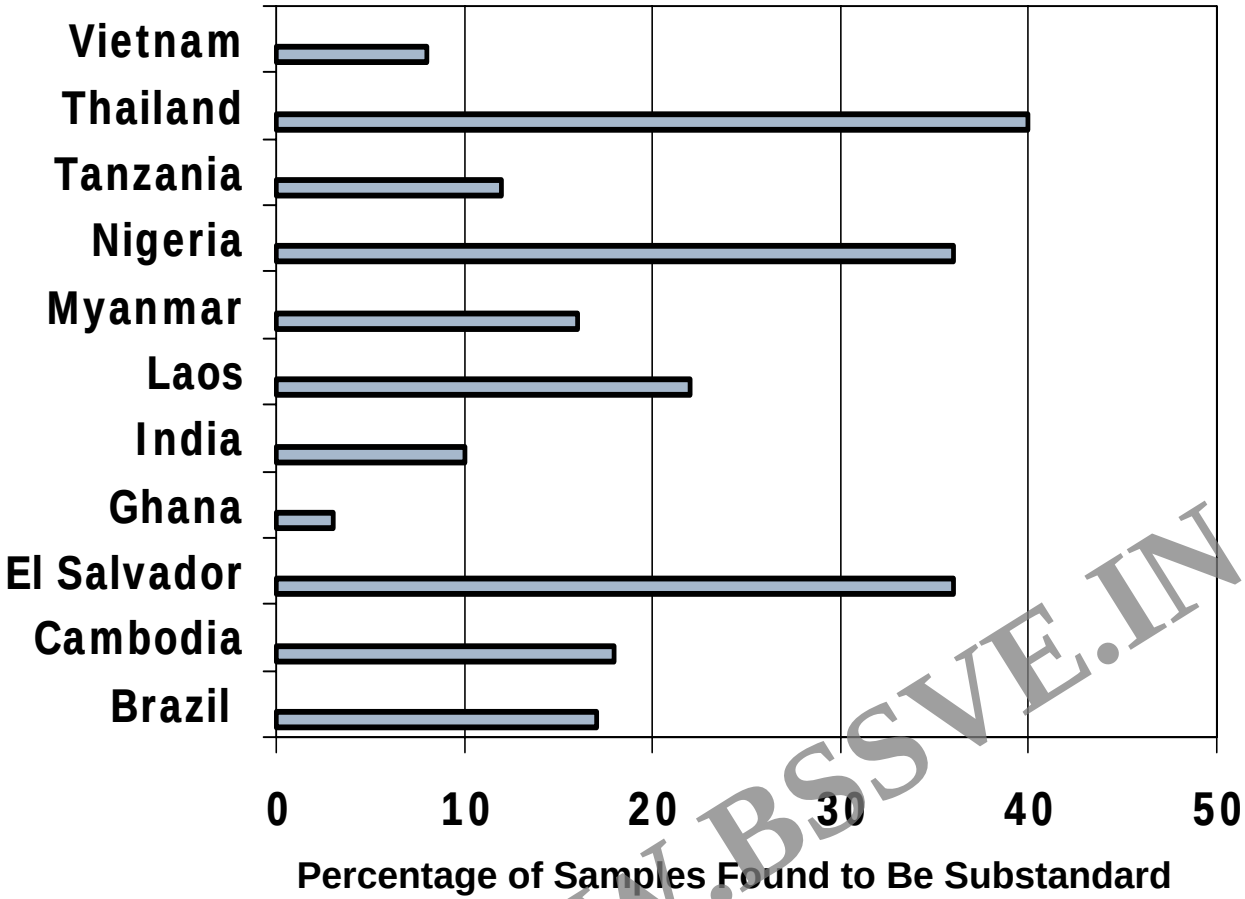
Substandard Medicines in Developing Countries



Percentage breakdown of data on 325 cases of substandard drugs—including antibiotics, antimalarials, and antituberculosis drugs—reported to WHO database from around the world

Rägo, L. 2002. *Ensuring Access to Drug Products That Are of Acceptable Quality.* PowerPoint presentation, WHO/EDM Technical Briefing, October 2, Geneva.

Substandard Medicines in Developing Countries



Therapeutic groups

- Analgesics
- Antihypertensives
- Antimicrobials
- Antimalarials

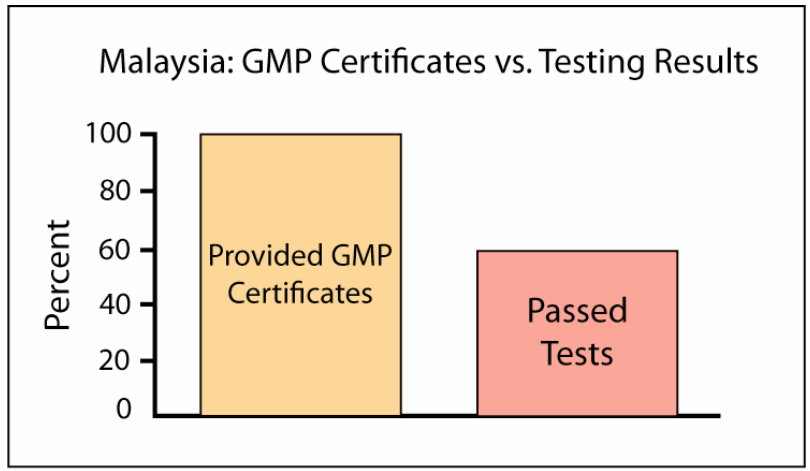
Rägo, L. 2002. *Ensuring Access to Drug Products That Are of Acceptable Quality.* PowerPoint presentation, WHO/EDM Technical Briefing, October 2, Geneva.

Quality Assurance: Product Testing

Malaysia

- Government Pharmaceutical Laboratory purchases in 1992

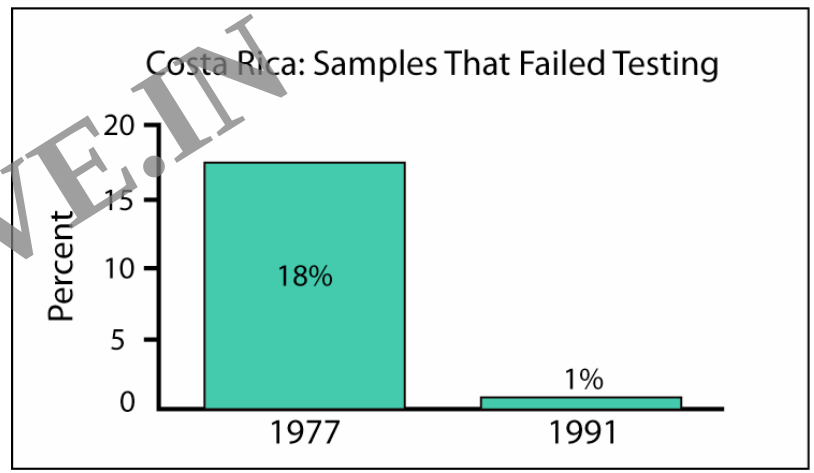
  GMP certification and product testing



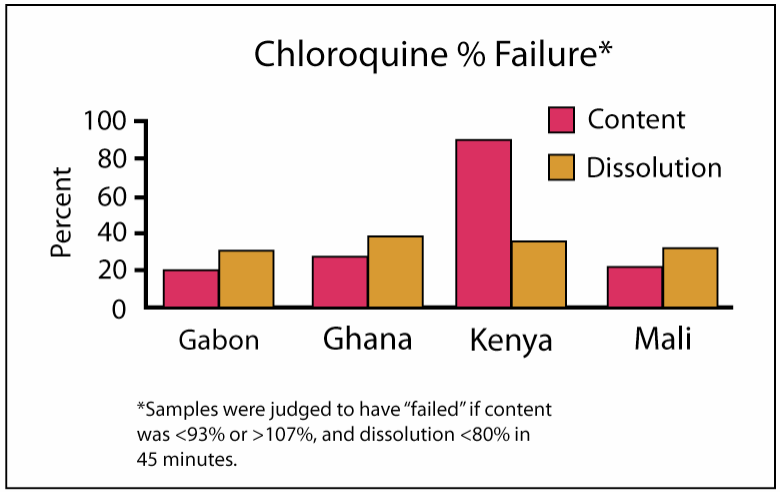
Costa Rica

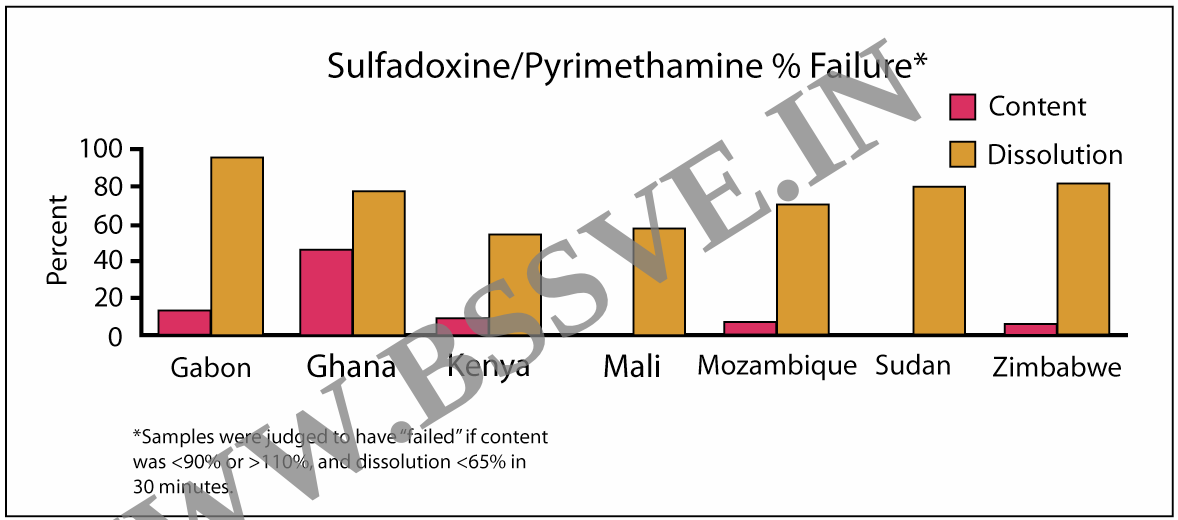
- Social Security Fund purchases in 1977 vs. 1991

  Product testing program



Quality of Antimalarial Products: Both Content & Dissolution Are Problems



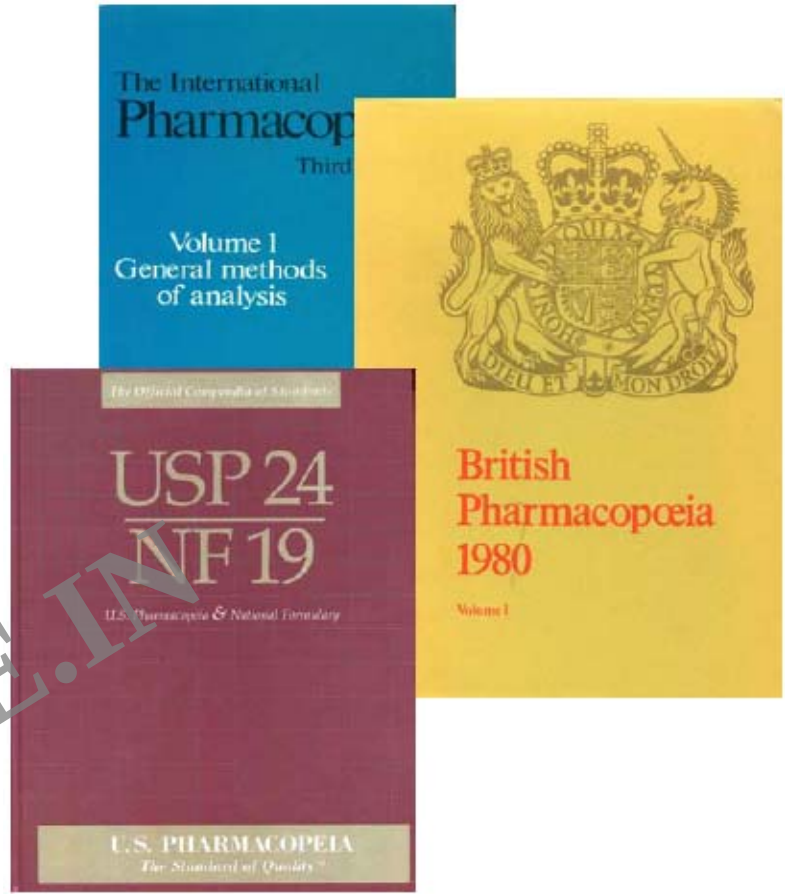


Current Testing Methods

- Color reactions
- Spectrophotometry
- Thin-layer chromatography (TLC)
- Gas chromatography
- High-performance liquid chromatography (HPLC)
- Others

Testing Standards and Methods

- Public vs. private standards (i.e., pharmacopeia vs. manufacturer/registration)
- Legal vs. credentialed methods (i.e., pharmacopeia vs. AOAC International)



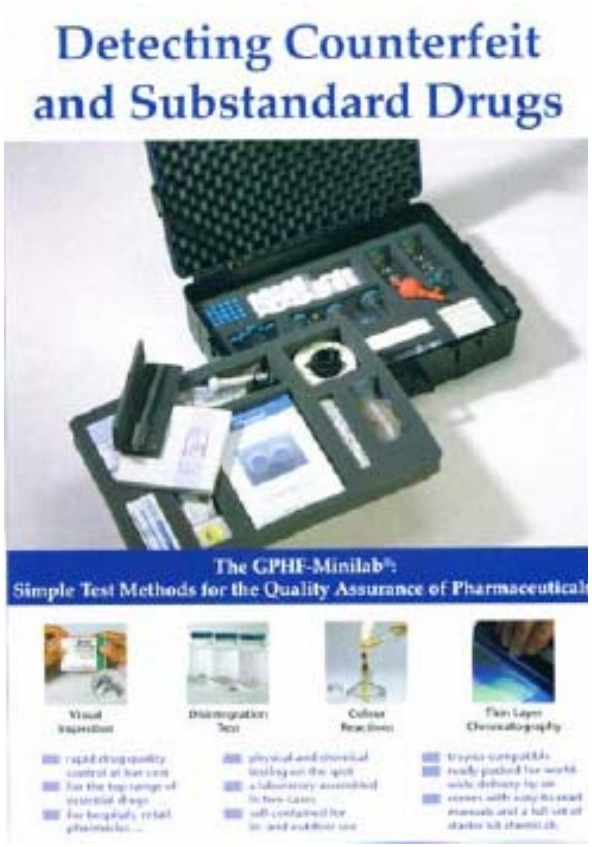
Pharmacopoeial Assessments

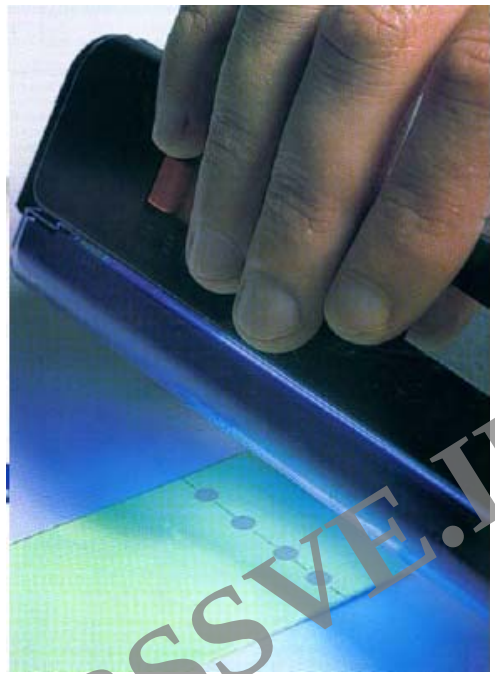
- Rooted in the analytical methods developed in the drug discovery process – technology dependent
- Discovery technologies are very focused on API and impurity characterization (high-resolution systems)
- Relatively expensive systems:
  - Analytical equipment
  - Maintenance and other consumables
  - Reference materials
  - Personnel training

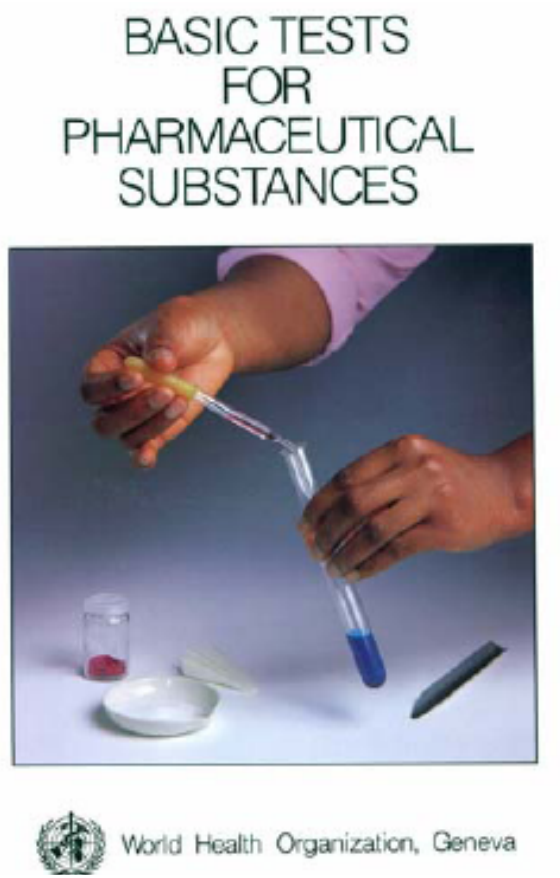
Implications for Resource-Limited Settings

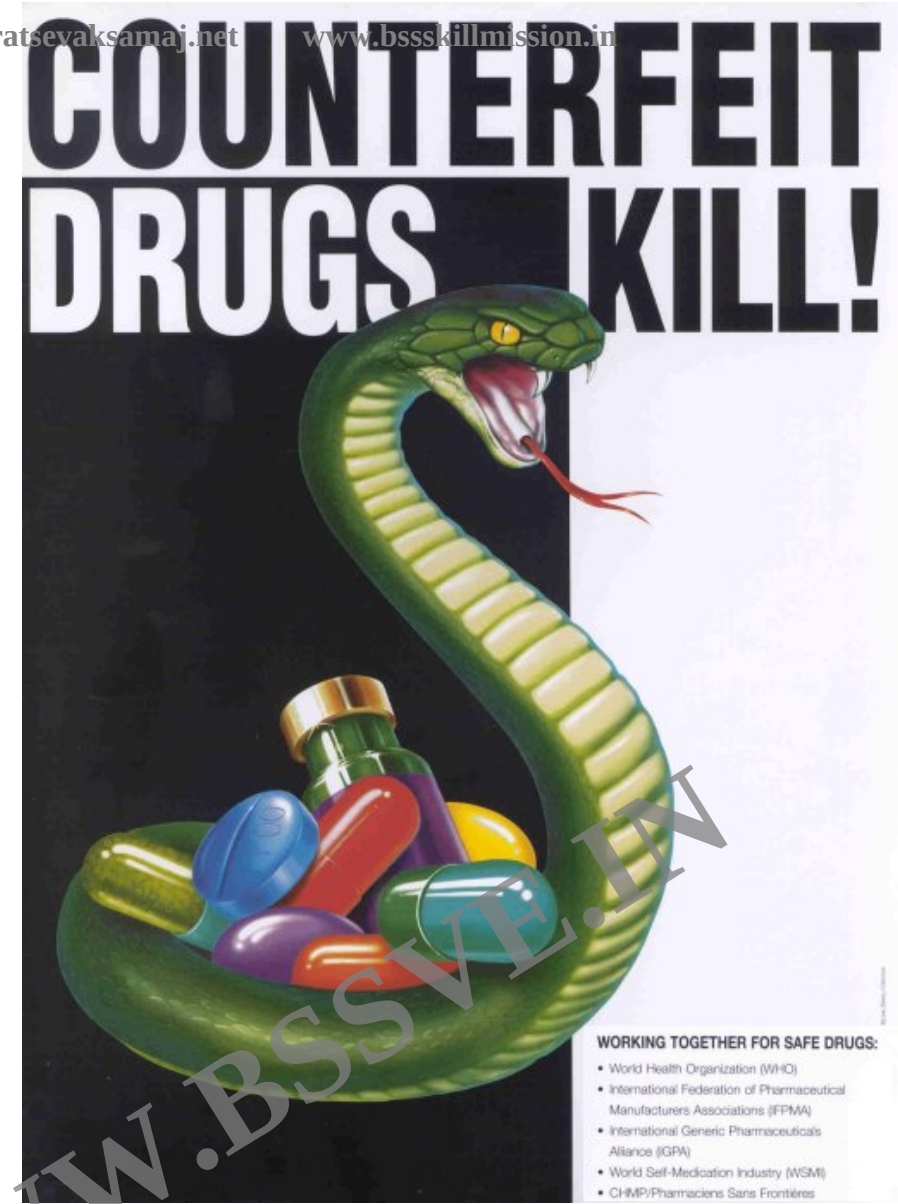
- Being largely import-dependent, developing countries need to develop and maintain an effective product testing program. Two major hurdles are:
  1. Newer essential therapeutic drugs for which public standards/monographs are not available
  2. Multisource essential therapeutic drug products for which the legal reference methods require high- technology support
- Difficult to implement and sustain effective high-technology testing programs:
  1. Complexity of equipment and maintenance needs
  2. Access to reference materials, reagents, and other consumables
  3. Need for highly trained technical staff
  4. Cost to launch and maintain effective program

Product Testing: Simple Methods









Source: World Health Organization

Global Problem

How Do Producers Counterfeit?

1. Specially manufactured counterfeits

   Sophisticated production facilities

   - Excellent labeling
   - All processes in-control

   Generally no active ingredient

2. Hacker manufactured counterfeits

   Poor quality products

   - Non-uniform Colors
   - Poor labeling
   - Poor compression – powder, capping

   Generally no active ingredient

Detection of Counterfeit Medicines

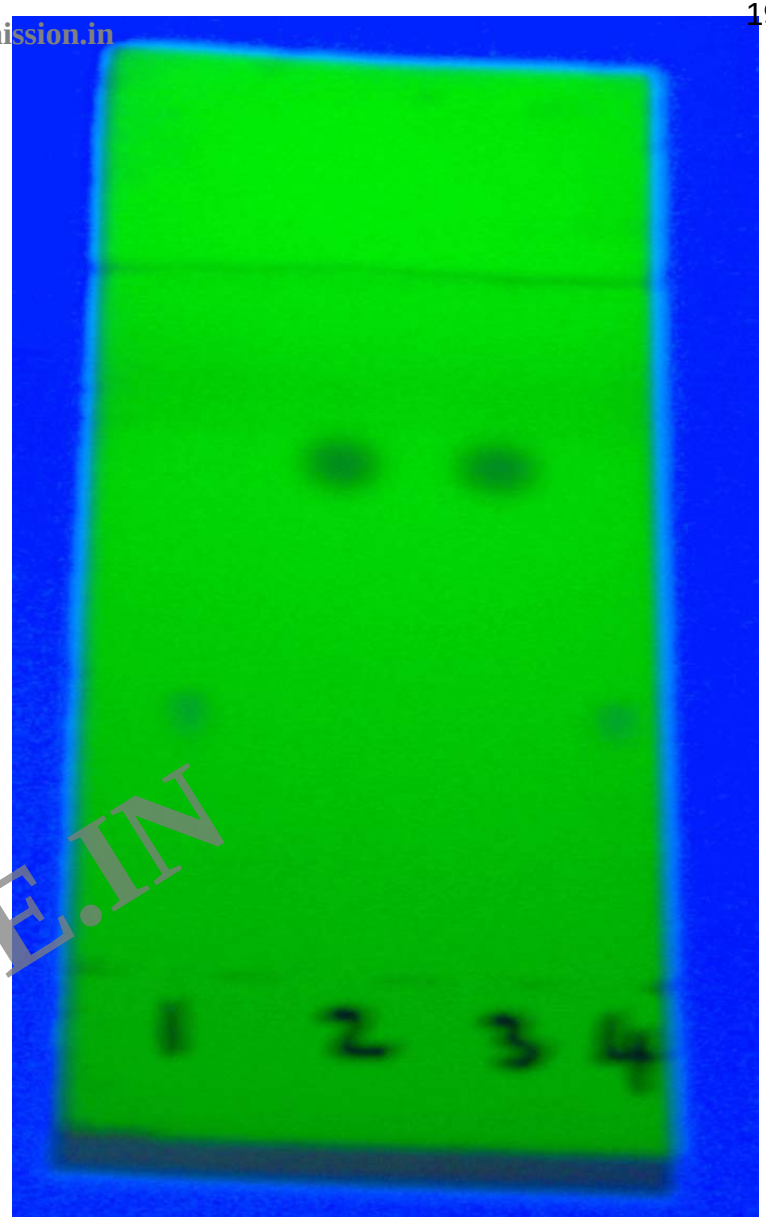
- A perfect counterfeit product cannot be detected.
- A well-made and well-labeled counterfeit is very difficult to detect even if direct comparisons between authentic and fake products can be made.
- Testing may be the best available option.

- Counterfeit Detection by TLC-- Wrong Drug
- Metronidazole

  Channel 1 = 100%

  Channel 4 = 80%
- Quinine

  Channels 2 & 3



Expired Chloroquine Injection Relabeled Quinine Dihydrochloride Injection

Photo courtesy of Thomas Layloff

Quality Assurance: Monitoring

- Product problem reporting
  - Suppliers
  - Health care providers
  - Consumers

- Supplier and product database
  - Supplier performance
  - Product problems
    - Clinical (ineffective, adverse events)
    - Pharmaceutical (physicochemical problems)

Quality Assurance: Evaluation and Enforcement

- Withdrawal of marketing authorization (product license)
- Delisting from prequalified status
- Rejection of shipment
- Product recall

Summary

- Many resource-poor countries are planning to purchase generics for ATM and other diseases, so product quality is becoming a growing concern

- There are a number of program implications if substandard or counterfeit products are purchased – poor treatment outcomes, potential liabilities, loss of public trust
- More open (international) procurement can be financially beneficial, but requires a more stringent QA system

- A three-tier testing program is a less expensive, viable option for quality control – big laboratories are not always necessary

Figure 14.3 Consumption-Based Forecast for an East Caribbean Country 6 month order

	Step 1			Steps 2 & 3	Step 4				Step 5	Step 6	Step 7	Step 8		Step 10	
Drug	Strength	BU	Pack Size	Total use in Period (BU)	Days Out of Stock	Adj Avg Mo.ly Use (BU)	Stock on Hand (BU)	Stock on Order (BU)	Safety Stock Level (BU)	Sugg'd Quantity to Order (BU)	Adj for Consumption Changes	Adj Order Quantity	Order Quantity (Packs)	Probable Pack Price ($USD)	Value of Proposed Order
Ampicillin	500 mg	capsule	1000	59500	0	9917	32000	42000	29750	45000		50737	51	69.3	3534.3
Ampicillin	250 mg	capsule	1000	89000	34	18218	81000	58000	54654	79617	81608	89769	90	35.1	3159
Ampicillin sodium injection	500 mg	ampoule	100	3879	0	647	111	7600	1940	48		53	1	29.95	29.95
Ampicillion suspension 100 mL	125 mg/5 mL	bottle	1	4128	0	688	1513	3000	2064	3743		4220	4220	0.75	3165
Antihistamine decongestatnt elixir	250 mL	bottle	1	853	29	169	351	929	507	747		843	843	1.57	1323.51
Antihistamine decongestant	(any)	tablet	500	50000	0	8333	0	62500	25000	37500		42281	85	12	1020
Basitracin antibiotic ointment	-----	tube	1	2414	31	484	34000	100	1453	-28288		2608	2608	0.54	1408.32
Bendrofluazide	5 mg	tablet	500	141500	30	28208	142000	50000	84623	146491		165168	330	1.9	627
Benzathine benzylpenicillin injection	2.4 M.U.	ampoule	50	1318	0	220	1486	0	659	1150		1297	26	25	650
Cephradine injection	500 mg	ampoule	100	2695	0	449	2300	1100	1348	1991		2244	22	75	1650
Chlorhexidine gluconate solution (Hibitan)	5%	liter	5	302	0	50	433	0	151	171		192	38	17.95	682.1
Chlorhexidine/centrimide (Savlon)	5 liter	liter	5	438	0	73	418	250	219	208		235	47	14.7	690.9
Chlorpropamide	250mg	tablet	1000	162000	0	27000	169000	0	81000	155000		174763	175	8.99	1573.25
Cimetidine (Tagamet) injection	200 mg	ampoule	10	1090	0	182	2580	0	545	-400		0	0	8.36	0
Cimetidine	400 mg	tablet	1000	24000	0	4000	23500	25000	12000	-500		0	0	42	0
Cloxacillin suspension 100 mL	125 mg/5 mL	bottle	1	882	0	147	1446	0	441	318		359	359	1	359
Cotrimoxazole suspension 100 Ml	00/40 mg/5 m	bottle	1	1152	0	192	374	1930	576	0		0	0	0.75	0
Cotrimoxazole	400/80 mg	tablet	1000	81000	0	13500	82000	0	40500	80000		90200	90	21	1890
Dextrose in saline (IV) 1000 mL	5% / 0.9%	bottle	1	1525	32	308	0	2288	924	1408		1588	1588	1.35	2143.8

Figure 14.3 Consumption-Based Forecast for an East Caribbean Country **6 Months Order**

$$Q_O = C_A * (LT + PP) + SS - (S_I + S_O)$$

	Step 1			Steps 2 & 3	Step 4				Step 5	Step 6	Step 7	Step 8		Step 10	
Drug	Strength	BU	Pack Size	Total use in Period (BU)	Days Out of Stock	Adj Avg Mo.ly Use (BU)	Stock on Hand (BU)	Stock on Order (BU)	Safety Stock Level (BU)	Sugg'd Quantity to Order (BU)	Adj for Consumption Changes	Adj Order Quantity	Order Quantity (Packs)	Probable Pack Price ($USD)	Value of Proposed Order
Ampicillin	500 mg	capsule	1,000.00	59,500.00	0.00	9,916.67	32,000.00	42,000.00	29,750.00	45,000.00		50,737.00	51.00	69.30	$3,534
Ampicillin	**250 mg**	**capsule**	**1,000.00**	**89,000.00**	**34.00**	**18,218**	**81,000**	**58,000.00**	**54,654.36**	**79,617**	**81,607.89**	**89,769**	**90.00**	**35.10**	**3,159.00**
Ampicillin sodium injection	500 mg	ampoule	100.00	3,879.00	0.00	646.50	111.00	7,600.00	1,940.00	47.50		53.00	1.00	29.95	29.95
Ampicillion suspension 100 mL	125 mg/5 mL	bottle	1.00	4,128.00	0.00	688.00	1,513.00	3,000.00	2,064.00	3,743.00		4,220.00	4,220.00	0.75	3,165.00
Antihistamine decongestatnt elixir	250 mL	bottle	1.00	853.00	29.00	168.94	351.00	929.00	507.00	747.44		843.00	843.00	1.57	1,323.51
Antihistamine decongestant	(any)	tablet	500.00	50,000.00	0.00	8,333.33	0.00	62,500.00	25,000.00	37,500.00		42,281.00	85.00	12.00	1,020.00
Basitracin antibiotic ointment	-----	tube	1.00	2,414.00	31.00	484.39	34,000.00	100.00	1,453.00	-28,287.51		2,608.00	2,608.00	0.54	1,408.32
Bendrofluazide	5 mg	tablet	500.00	141,500.00	30.00	28,207.52	142,000.00	50,000.00	84,623.00	146,490.65		165,168.00	330.00	1.90	627.00
Benzathine benzylpenicillin injection	2.4 M.U.	ampoule	50.00	1,318.00	0.00	219.67	1,486.00	0.00	659.00	1,150.00		1,297.00	26.00	25.00	650.00
Cephradine injection	500 mg	ampoule	100.00	2,695.00	0.00	449.17	2,300.00	1,100.00	1,348.00	1,990.50		2,244.00	22.00	75.00	1,650.00
Chlorhexidine gluconate solution (Hibitan)	5%	liter	5.00	302.00	0.00	50.33	433.00	0.00	151.00	171.00		192.00	38.00	17.95	682.10
Chlorhexidine/centrimide (Savlon)	5 liter	liter	5.00	438.00	0.00	73.00	418.00	250.00	219.00	208.00		235.00	47.00	14.70	690.90
Chlorpropamide	250mg	tablet	1,000.00	162,000.00	0.00	27,000.00	169,000.00	0.00	81,000.00	155,000.00		174,763.00	175.00	8.99	1,573.25
Cimetidine (Tagamet) injection	200 mg	ampoule	10.00	1,090.00	0.00	181.67	2,580.00	0.00	545.00	-400.00		0.00	0.00	8.36	0.00
Cimetidine	400 mg	tablet	1,000.00	24,000.00	0.00	4,000.00	23,500.00	25,000.00	12,000.00	-500.00		0.00	0.00	42.00	0.00
Cloxacillin suspension 100 mL	125 mg/5 mL	bottle	1.00	882.00	0.00	147.00	1,446.00	0.00	441.00	318.00		359.00	359.00	1.00	359.00
Cotrimoxazole suspension 100 Ml	00/40 mg/5 m	bottle	1.00	1,152.00	0.00	192.00	374.00	1,930.00	576.00	0.00		0.00	0.00	0.75	0.00
Cotrimoxazole	400/80 mg	tablet	1,000.00	81,000.00	0.00	13,500.00	82,000.00	0.00	40,500.00	80,000.00		90,200.00	90.00	21.00	1,890.00
Dextrose in saline (IV) 1000 mL	5% / 0.9%	bottle	1.00	1,525.00	32.00	308.03	0.00	2,288.00	924.00	1,406.27		1,588.00	1,588.00	1.35	$2,143.80
															$23,906.13

Cell Names
Adjusted Average Monthly Use = G5
Total Period Use = E5
Stock on Hand = H5
Stock on Order = I5
Days Out of Stock = F5

Order_Quant_Packs = N5
Pack Price = O5

Ampicillin_250_Value = P5

Probable Pack Price	Value of Order
	$3,159
$34	
$35	
$36	
$37	