Use of research for clinical practice and policies

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World Health Organization

A day at WHO…

World Health Organization

- **Are there effective ways of identifying women at increased risk of postpartum haemorrhage antenatally?**
- **Which of oxytocin/ ergometrine/ misoprostol / sulprostone / other prostaglandins / carbetocin/ traditional Chinese medicines is most effective for treatment of PPH?**
- **What options can be recommended for treatment of XDR-TB?**
- **In the context of scaling up access to antiretrovirals, what clinical tasks can be carried out by non-physicians?**
- **What are appropriate quality standards for the manufacture of herbal medicines?**
- **How do you improve the quality of trauma care [in LMIC]?**

Evidence…

Are there effective ways of identifying women at increased risk of postpartum haemorrhage antenatally?	Maybe..
Which of oxytocin/ ergometrine/ misoprostol / sulprostone / other prostaglandins / carbetocin/ traditional Chinese medicines is most effective for treatment of PPH?	Yes (for some)
What options can be recommended for treatment of XDR-TB?	Not yet
In the context of scaling up access to antiretrovirals, what clinical tasks can be carried out by non-physicians?	Maybe
What are appropriate quality standards for the manufacture of herbal medicines?	Maybe
How do you improve the quality of trauma care? [in LMIC]	Probably not


World Health Organization
GUIDELINES FOR THE TREATMENT OF MALARIA
Policy Makers and Health Professionals
PREVENTION
THE INTERAGENCY LIST OF ESSENTIAL MEDICINES FOR REPRODUCTIVE HEALTH
2006
GUIDELINES
MANAGEMENT OF THE CHILD WITH A SERIOUS INFECTION OR SEVERE MALNUTRITION
Guidelines for care at the first referral level in developing countries
POCKET BOOK OF
Hospital care for children
GUIDELINES FOR THE MANAGEMENT OF COMMON ILLNESSES WITH LIMITED RESOURCES
World Health Organization
World Health Organization

Problem:
Oxman, Lavis & Fretheim, Lancet. 2007;369(9576):1883-9.

- **WHO guidelines are insufficiently transparent and not evidence based**
  - **Lack of use of systematic reviews**
  - **Lack of transparency about judgements**
  - **Too much dependence on expert opinion**
  - **Lack of emphasis on adapting global guidelines to end users' needs**
  - **Tension between time taken and when advice needed**
  - **Lack of resources**

Process for developing recommendations

- More about expert consensus
- Less about evidence and specifically less about systematic reviews
- Relatively little use of central support function and guidelines for guidelines to ensure methodological rigour
- Relatively little formalization of the recommendation development process
- Constrained often by a lack of resources and the urgency of the need

More about expert consensus

- Expert committees – heavy reliance on ’world experts’
- Sometimes little insight into shortcomings, variable preparation
- Consensus process can be dominated by strong person at the table
- Variation in consultation processes – who is consulted, why
- Cultural change from GOBSAT needs support

Solution

- **WHO Guidelines Review Committee**
  - **Approval and review process**
  - **Standards for use of evidence**
  - **Tailored types of guidelines**
  - **Standards for reporting**
  - **Regular review and update**

Minimum standards for *reporting* in WHO guidelines

- Who was involved and their declaration of interests
- How the guideline was developed, including
  - how the evidence was identified
  - how the recommendations were made
- Use by date (review by date)

Use of evidence

- Systematic identification of all relevant evidence
- Quality assessment and grading
- Explicit link between evidence and recommendations

So….

- **Is simvastatin an essential medicine?**

- **Essential medicines are those that satisfy the priority health care needs of the population. Selection of essential medicines therefore needs to take account of public health relevance, the best available clinical evidence of efficacy and safety as well as an assessment of comparative cost-effectiveness.**

Table 5: Effectiveness of statins in three RCTs of secondary CHD Prevention, expressed using absolute measures of risk reduction:

Study/Outcome	Risk in Placebo Arm	ARR (95% CI)	NNT (95% CI)
4S (Simvastatin)			
All-cause mortality	11.52	3.32 (1.57 to 5.07)	31 (19.7 to 63.6)
CHD mortality	8.5	3.50 (2.03 to 4.98)	29 (20.1 to 49.2)
Total stroke	n/a		
CHD mortality + nonfatal MI	27.98	8.57 (6.09 to 11.06)	12 (9.0 to 16.4)
CARE (Pravastatin)			
All-cause mortality	9.43	0.78 (-0.96 to 2.53)	ns
CHD mortality	5.73	1.11 (-0.23 to 2.46)	ns
Total stroke	3.66	1.16 (0.11 to 2.21)	87 (45.3 to 915.6)
CHD mortality + nonfatal Mi	13.19	3.00 (1.05 to 4.95)	34 (20.2 to 95.5)
LIPID (Pravastatin)			
All-cause mortality	14.06	3.02 (1.66 to 4.39)	34 (22.8 to 60.4)
CHD mortality	8.29	1.92 (0.85 to 3.00)	52 (33.3 to 117.7)
Total stroke	4.53	0.79 (-0.04 to 1.61)	ns
CHD mortality + nonfatal MI	15.88	3.54 (2.10 to 4.97)	29 (20.1 to 47.6)

Absolute Risk Reduction (ARR) and Numbers Needed to Treat (NNT).
ns = not statistically significant

Uncertainties

- Requirement for biochemical monitoring?
- Use in diverse settings, with limited resources?
- Ability to mage use to be cost-effective?

- Recommendation?

or ….

- **What should be recommended as pharmacological management of opioid dependence?**

GRADE Evidence Profile

Author(s): Amato L
Date: 02/02/2006 16.01.56
Question: Should methadone vs buprenorphine be used in all opioid dependent patients?
Patient or population: any opioid dependent patients wishing to detox
Settings: outpatients
Systematic review: Gowing. Buprenorphine for the management of opioid withdrawal Amato Methadone at tapered doses for the management of opioid withdrawal

Quality assessment						Summary of findings					
						No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Consistency	Directness	Other considerations	metha done	buprenor phine	Relative (95% CI)	Absolute (95% CI)		
completion of treatment (number of people that completed the treatment Follow up: 14 to 30 days)											
2	Randomised trials	No limitations	No important inconsistency	Some uncertainty (-1)[1]	Imprecise or sparse data (-1)[1]	21/30 (70%)	26/33 (78,8%)	RR 0.88 (0.67 to 1.15)	100/1 000 (290 less to 100 more)	⨁⨁◯◯ Low	1
side effects (objective measures Range: to . Better indicated by: lower scores)											
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[4]			-	WMD -5.1[3] (-14 to 5.3)	⨁⨁⨁◯ Moderate	1

Footnotes:

imprecise or sparse data
imprecise or sparse data: only 63 patients
difference in systolic blood pressure
only one study with 39 patients

Uncertainty

- 2 trials, developed world
- Very specific settings
- Resources required
- Acceptability globally
- Availability of product
- Skilled providers

- Recommendation?

Policy recommendations are harder…

- Can nurses provide adequate care for patients with HIV?

- Evidence
  - McPherson et al, 2006
  - 21/355 included studies
  - No quantitative data on patient outcomes
  - No conclusions
- Recommendation?

What about neglected populations?

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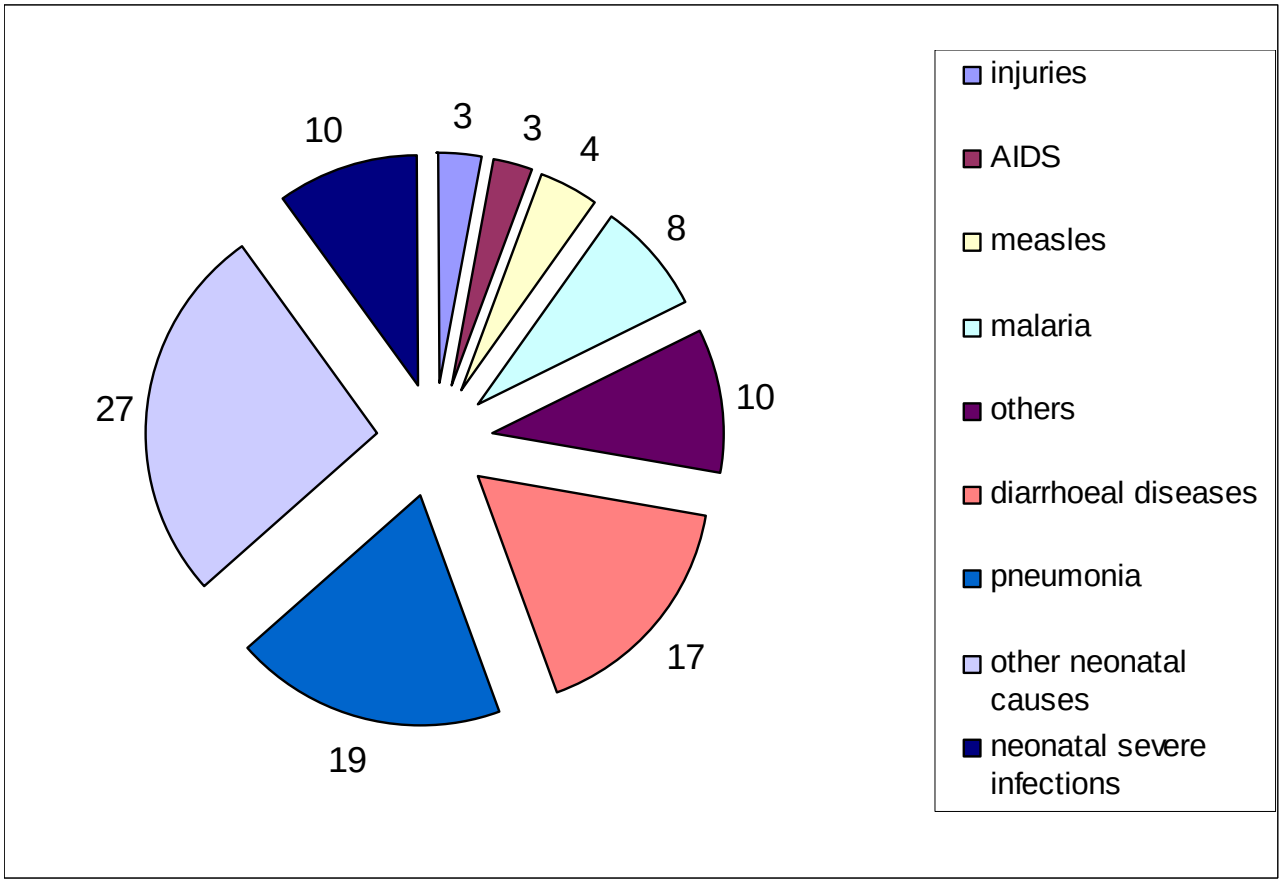
Causes of death in under 5s



World Health Report, 2005

First list of essential medicines for children

- Children up to 12 years of age
- Including neonates
  - → oral liquid forms, noting problems with them
- For consistency, based on EML 15

  may be missing some specific diseases, generally covers burden of disease
- Problem with paucity of data
  - → Need to indicate known limitations of data and restrictions

Very high priority research questions

#	Question/topic	priority	feasibility	Existing reviews?
25	Review of medicines used for TB in children, including evidence regarding dose, and alternatives for streptomycin (Section 6.2.4).	33	No	No
26	Drugs for second-line treatment of TB (MDR-TB) in children (Section 6.2.4).	26	No	No
16	Evidence of efficacy and safety of use of anthelminth/antifilarial/antischistosomal and antitrematode medicines in children below the licensing age limits (Section 6.1).	26	No	Some
18	Application for inclusion of oral cephalosporin for use in children (indications include UTI, osteomyelitis) (Section 6.2.1).	26	Yes	Yes
27	Efficacy, safety, place in therapy of rifabutin and rifapentin in management of TB with HIV co-infection in children (Section 6.2.4).	24	No	No
67	Place in therapy of oral salbutamol preparations in children, with particular emphasis on efficacy and safety in asthma and in the wheezy child with acute respiratory tract infection (Section 25.1).	22	Yes	1 RCT identified

Highly feasible reviews/ studies

- use of cephalosporins
- rifabutin and rifapentin for TB co-infection in HIV
- efficacy of oral salbutamol preparations
- use of ipratropium and long-acting beta agonists in respiratory disease
- antidotes
- use of fluoroquinolones in children (review of the toxicity of fluoroquinolones)
- use of diazepam and alternatives such as midazolam in children
- choice of macrolides in children (comparative safety and efficacy of macrolides, if erythromycin is used which salt, use in neonates)
- use of ibuprofen
- review of anticonvulsants particularly newer agents
- role of intravenous sodium valproate for status epilepticus
- choice of laxatives in children
- Antihelminths – efficacy and saftey in under 4's
- antitrematode medicines
- oncology medicines – what is the minimum package?

Table 1. Prospective Controlled Trials of Benznidazole or Nifurtimox for Chronic Chagas Disease in the Published Literature

Source	Chagas Form	Study Design	Age, y	Length of Treatment, d	Comparison Groups	Sample Size, No.	Primary Outcome of Interest, %	Major Adverse Events or Adverse Effects >5%
de Andrade et al,[87] 1996[a]	Indeterminate (n = 120) Early Chagas heart disease (n = 9)[b]	Randomized, double-blinded	7-12	60			Negative seroconversion at 36 mo by AT-ELISA	Maculopapular rash and pruritus
					Benznidazole, 7.5 mg/kg per d	64	58	12.5
					Placebo	65	5	3.1
Sosa Estani et al,[88] 1998	Indeterminate	Randomized, double-blinded	6-12	60			Negative seroconversion at 48 mo by F29-ELISA	Intestinal colic
					Benznidazole, 5 mg/kg per d	55	62	NR
					Placebo	51	0	NR
							Xenodiagnosis-positive at 48 mo	
					Benznidazole, 5 mg/kg per d	55	5	NR
					Placebo	51	51	NR
Coura et al,[89] 1997[c]	Indeterminate with ≥2 of 3 pretreatment xeno-diagnoses positive[d]	Randomized but apparently not double-blinded	Adults[d]	30	Benznidazole, 5 mg/kg per d	26	Posttreatment xeno-diagnosis positive 1.8	NR
					Nifurtimox, 5 mg/kg per d	27	9.6	NR
					Placebo	24	34.3	NR
Viotti et al,[90] 2006[d]	Indeterminate and nonsevere determinate	Alternate assignment to benznidazole or no treatment; nonrandomized, unblinded	Mean, 39.4	30			Progression	Severe allergic dermatitis prompting discontinuation
					Benznidazole, 5 mg/kg per d	283	4.2	13.0
					No treatment	283	14.1	NR
					Benznidazole, 5 mg/kg per d	283	Mortality 1.1	NR
					No treatment	283	4.2	NR

Abbreviations: AT-ELISA, Antigen trypomastigote chemoluminescent enzyme-linked immunosorbent assay; CI, confidence interval; ECG, electrocardiogram; HR, hazard ratio (mortality adjusted for ejection fraction); F29-ELISA, flagellar calcium binding protein F29-antigen–based enzyme-linked immunosorbent assay; IFA, indirect immunofluorescence assay; IHA, indirect hemagglutination; NR, not reported.

[a] Efficacy, 55.8% (95% confidence interval, 40.8%-67.0%) by intention-to-treat analysis based on AT-ELISA results.

[b] All children were asymptomatic but 9 had right bundle-branch block on ECG; no difference in distribution in treatment vs placebo groups.

[c] Neither age nor clinical findings reported in article; presumed to have the indeterminate form.

[d] Chagas cardiac disease Kuschnir grades I or II; those with grade III, defined by presence of heart failure, were excluded. Distribution at study entry: 63.6% Kuschnir 0, 26.1% grade I, 10.2% grade II. See Box for definition of Kuschnir grades. Median follow-up, 9.8 years.

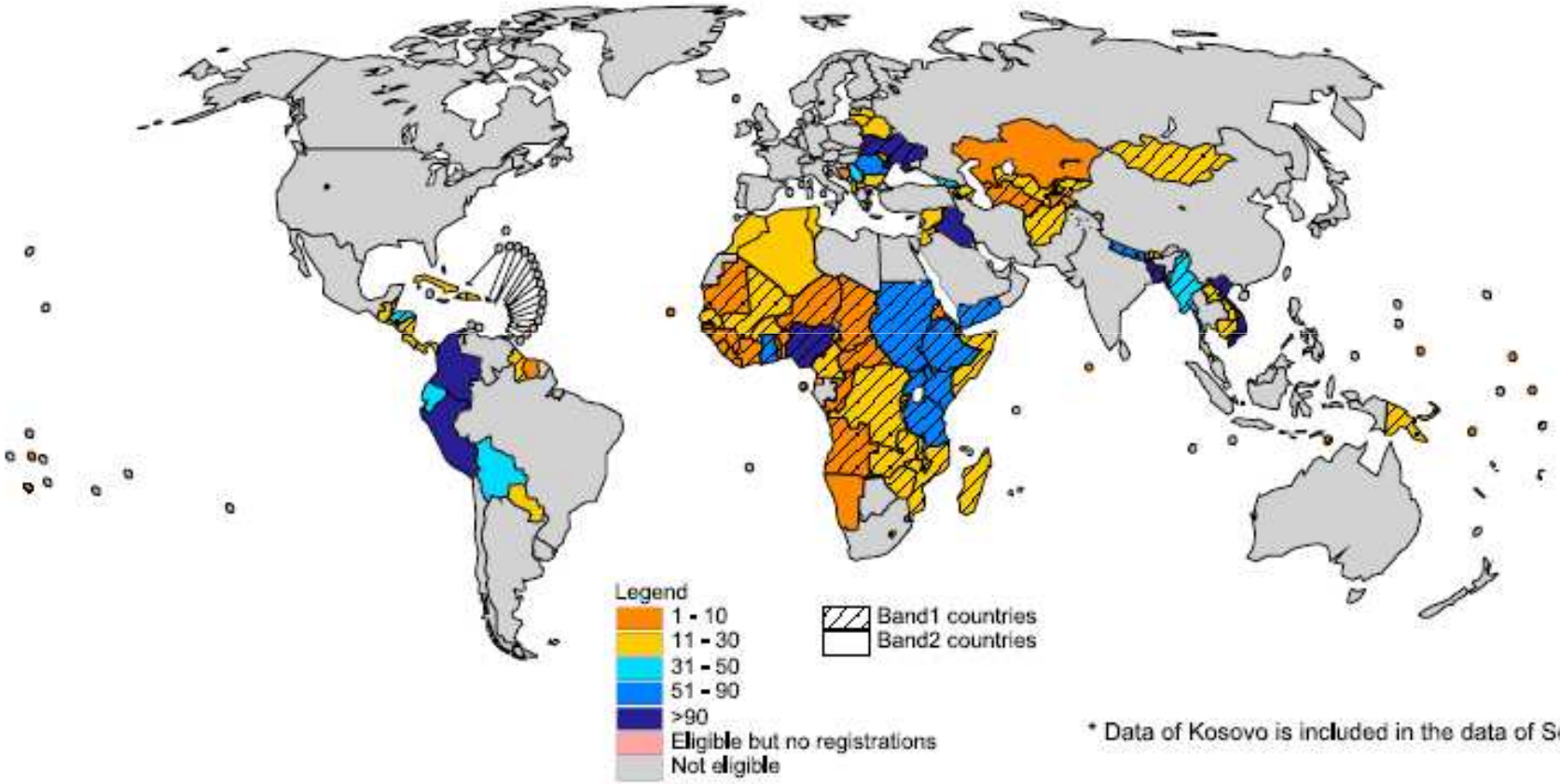
Bern et al, JAMA. 2007;298(18):2171-2181

World Health Organization

At country level….

- Access to information
- Cost
- Capacity
- Local research

Institutions registered with HINARI *



* Data of Kosovo is included in the data of Serbia

30.01.2007

Challenges

- Making global recommendations without global evidence
- Access to existing evidence
- Audience
  - Policy makers
  - Clinicians
  - Everyone in between
- Implementation and adaptation at country level
- Evaluation
- Updating

Thank you

www.who.int/medicines

World Health Organization