The WHO/IUATLD Supra-National Reference laboratory network for tuberculosis

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- History and overview of the project
- SRLN current status and Terms of Reference
- 10th round of proficiency testing
- Contribution to TB control

SRL History

Created in 1994

- support global drug resistance surveillance (DRS)

The Global Project on Anti-TB Drug Resistance Surveillance

Objectives

- Estimate the magnitude of drug resistance globally
- Determine trends
- Provide data to inform policy decisions
- Evaluate the progress of TB programmes
- Strengthen laboratory networks

Publications:

Guidelines for surveillance of drug resistance in tuberculosis.
revision (1997/2006)

Global Reports:
1st report: 1997 → 35 settings
2nd report: 2000 → 58 settings
3rd report: 2004 → 77 settings

WHO / IUATLD Global Project coverage 1994 - 2002

Time surveyed

1

2

3 or more

No data

0 2000 4000 Kilometers

Data Source: WHO/IUALTD Global Project
Map Production:
Public Health Mapping Group
Communicable Diseases (CDS)
World Health Organization

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Prevalence of MDR-TB among new cases 1994 - 2002

Data Source: WHO/IUALTD Global Project
Map Production:
Public Health Mapping Group
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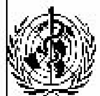

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The Global Project on Anti-TB Drug Resistance Surveillance

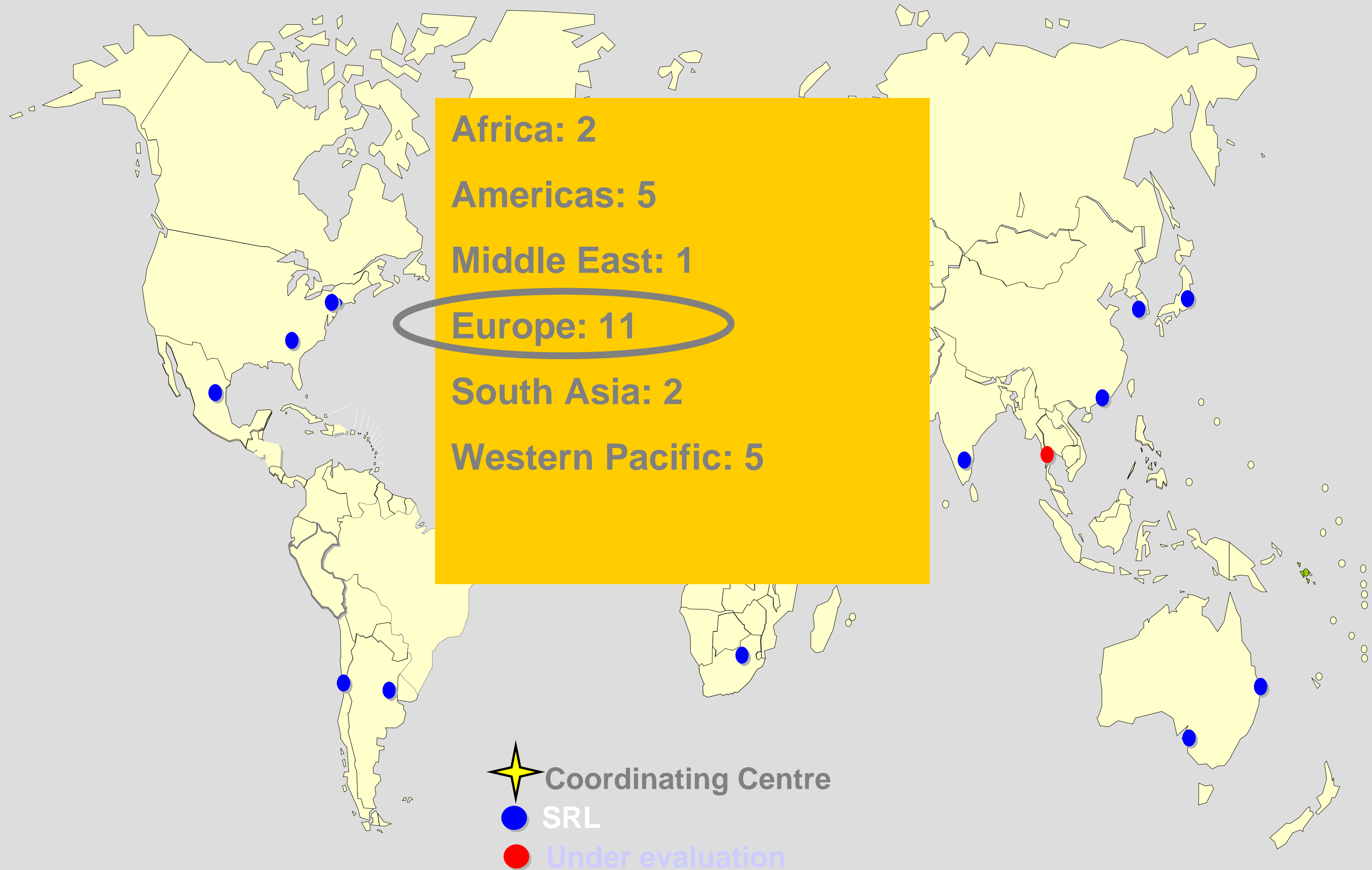
Principles:

- Accurate sampling represents population under study
- Differentiation between new and previously treated cases
- Quality assured laboratory results

SRL History (cont.)

- Originally 16 laboratories
  - no proper selection criteria
    - quality assurance + links with higher-prevalence countries
    - selection monopolised by WHO
      (exclusive source of finance)
  - heavy concentration in Europe
    - low-income: only 2 labs (India)
      extreme scarcity of good laboratories
    - new SRL being certified (middle income)
- Now 26 laboratories

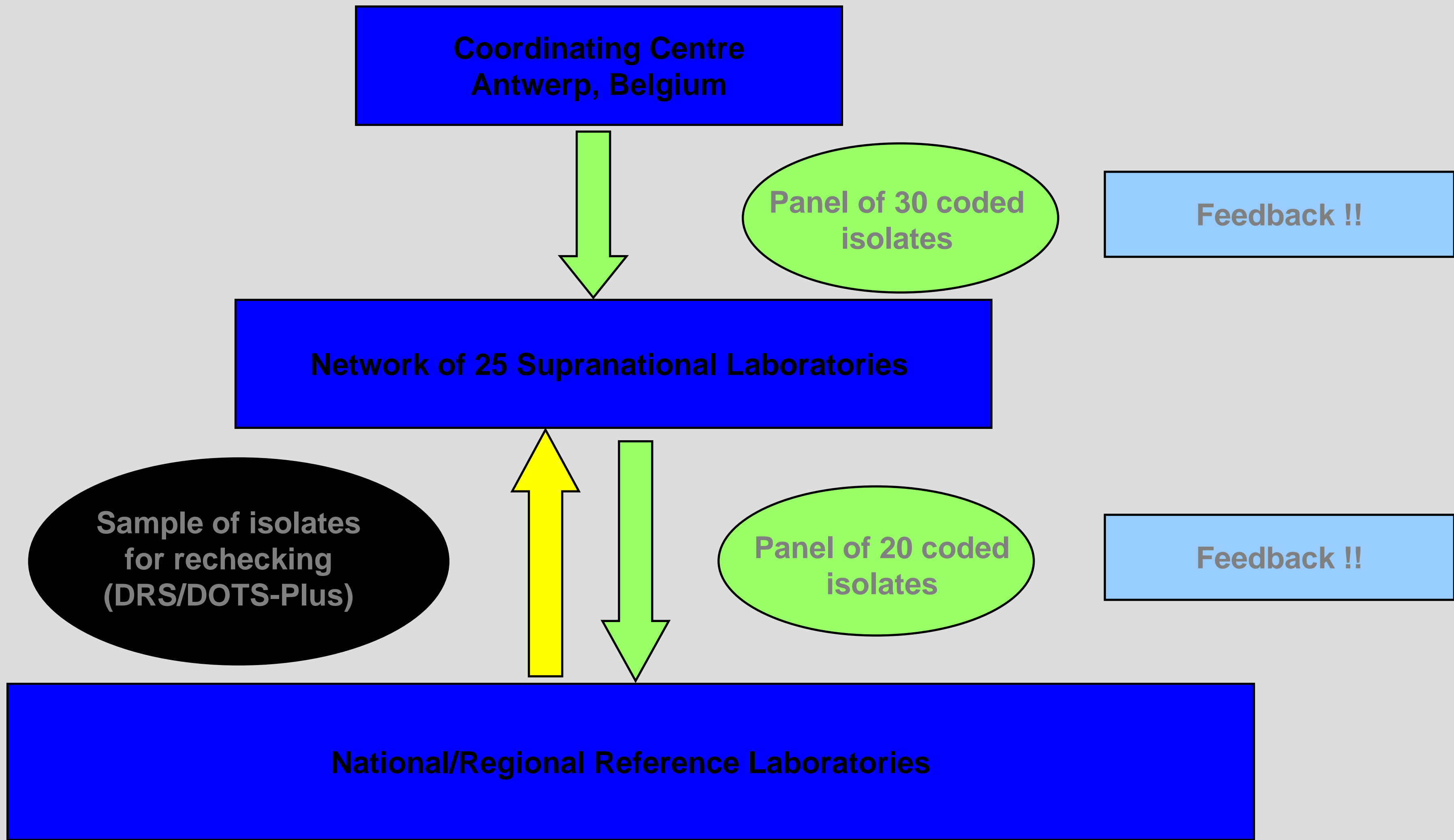
The Supranational Laboratory Network (SRLN) 2005 (links with >150 countries)



SRL Terms of reference

- Permanent functional laboratory
- Commitment to support at least two countries
  - PT
  - QA of surveys / DOTS-Plus
  - Training where necessary
- Commitment to participate in meetings/studies
  - 5 annual network meetings
  - 2 SLD studies ongoing
- Participate in annual EQA (PT), fulfil performance criteria

The SRL Network
SYSTEM OF EXTERNAL QUALITY ASSURANCE



Organization of proficiency testing

- Coordinating laboratory:
  - rounds 1 to 5 by Ottawa, Canada: succeeded in
    - standardization of techniques
    - validation of methods
    - improved precision
  - rounds 6 to 11: Antwerp, Belgium: continuation
    - Expansion to 24 laboratories

Panel constitution

- 20 strains
  - 10 of those in duplicate : reproducibility analysis
  - attain significance after two successive rounds (LQAS)

    no error: 95% efficiency reached

    max. 2 errors: 90% efficiency reached
- Panel targets
  - 50% prevalence of resistance (any drug)
  - non-MDR subset
  - various combinations of resistance
  - clinically well documented
  - extensive pre-testing

SRL EQA: RESULTS ROUND 10

		No. of labs with results in the range of					Average
		100%	95-99%	90-94%	80-89%	<80%	score
ISONIAZID	Sens.	20	0	1	0	0	100%
(19 R, 9 S / 2?)	Spec.	20	0	0	0	1	99%
	Effic.	19	1	1	0	0	99%
RIFAMPICIN	Sens.	19	0	2	0	0	99%
(15 R, 13 S / 2?)	Spec.	13	0	2	5	1	94%
	Effic.	13	1	6	0	1	97%
STREPTOMYCIN	Sens.	14	0	4	3	0	97%
(18 R, 10 S / 2?)	Spec.	14	0	4	1	2	95%
	Effic.	10	4	5	2	0	96%
ETHAMBUTOL	Sens.	8	0	0	6	7	83%
(6 R, 16 S / 8?)	Spec.	6	2	4	7	2	92%
	Effic.	0	2	9	9	1	89%

Summary results Round 5 to 10

	INH	Rifampicin	Streptomycin	Ethambutol
Results evaluated				
total	2391	2106	2091	2099
range individual labs	73 - 117	65 - 103	66 - 102	65 - 103
Sensitivity				
average	100%	100%	96%	94%
range individual labs	97 - 100%	93 - 100%	76 - 100%	34 - 100%
Specificity				
average	99%	99%	99%	98%
range individual labs	97 - 100%	90 - 100%	84 - 100%	90 - 100%
Efficiency				
average	99%	99%	97%	96%
range individual labs	97 - 100%	93 - 100%	86 - 100%	79 - 100%
# of SRL reaching 90-95% efficiency				
calculated	ALL 21	20 / 21	17 / 21	19 / 21
LQAS assured	17	18	17	17

SRL proficiency looks good

- Over time persistent excess errors:

  isoniazid: none

  rifampicin: one laboratory

  streptomycin: one laboratory

  ethambutol: two laboratories

- Excess errors
  - not linked to specific methods
  - periodically seen in several labs
    - systematic: changed detail of technique ?
    - random: manipulation errors

But may be over-estimated

- Judicial result criterion
  - evaluating precision, not necessarily accuracy ?
  - forces to exclusion of problem strains
- Strains excluded (<80% agreement)

  round 6 to 10
  - isoniazid: 2
  - rifampicin: 9
  - streptomycin: 10
  - ethambutol: 11

Samples for rechecking DRS

- Limitations
  - international transport of TB strains
  - lack of funding
  - Africa: links with SRL not clearly defined + vague / scattered over different SRL

Network contribution to TB control

- Drug resistance surveillance
  - better standardization of testing
  - quality assurance of surveys
  - more reliable data available

Data on New cases 2006

no data

estimates

sub-national surveys

countrywide surveys

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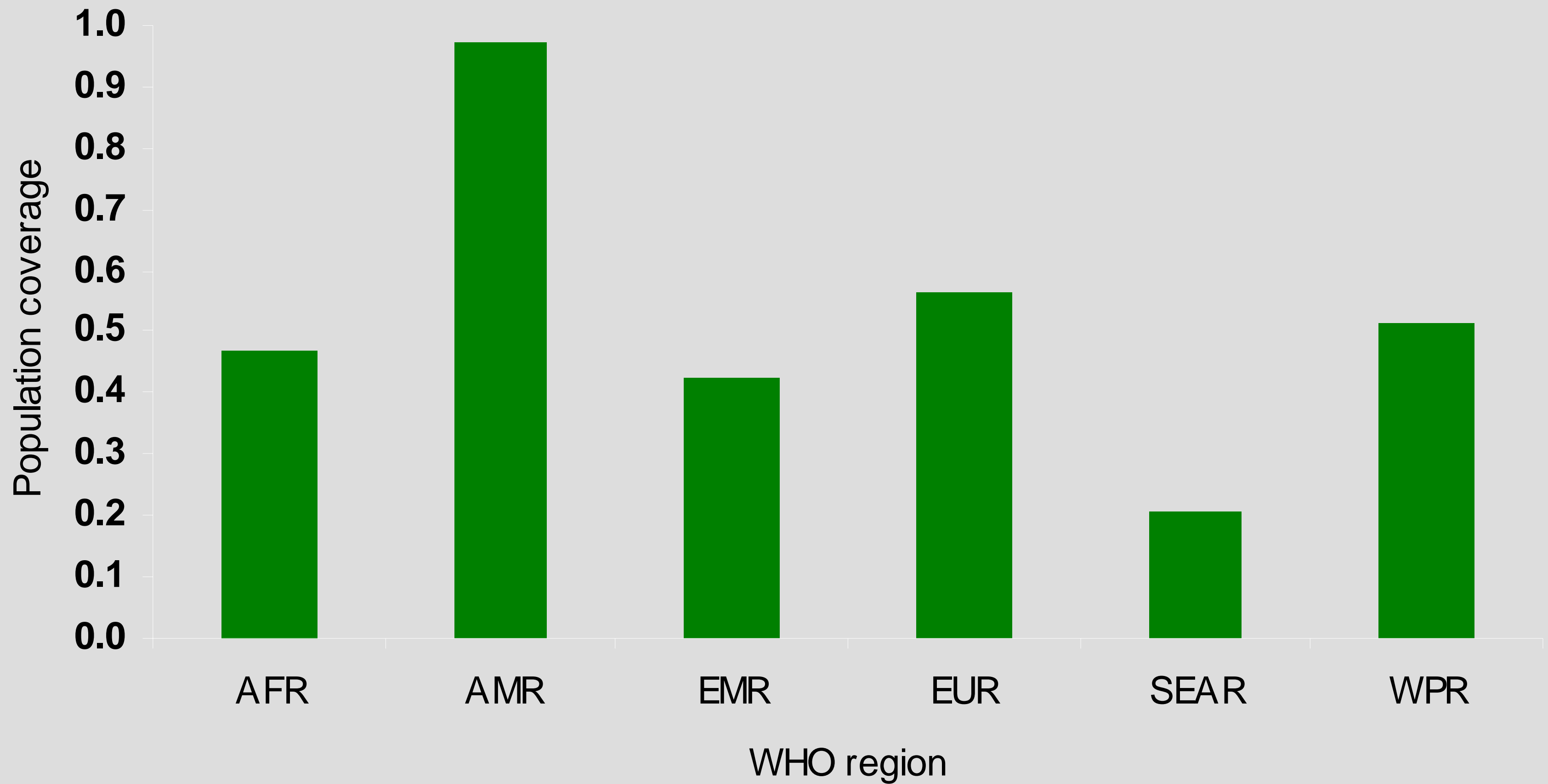
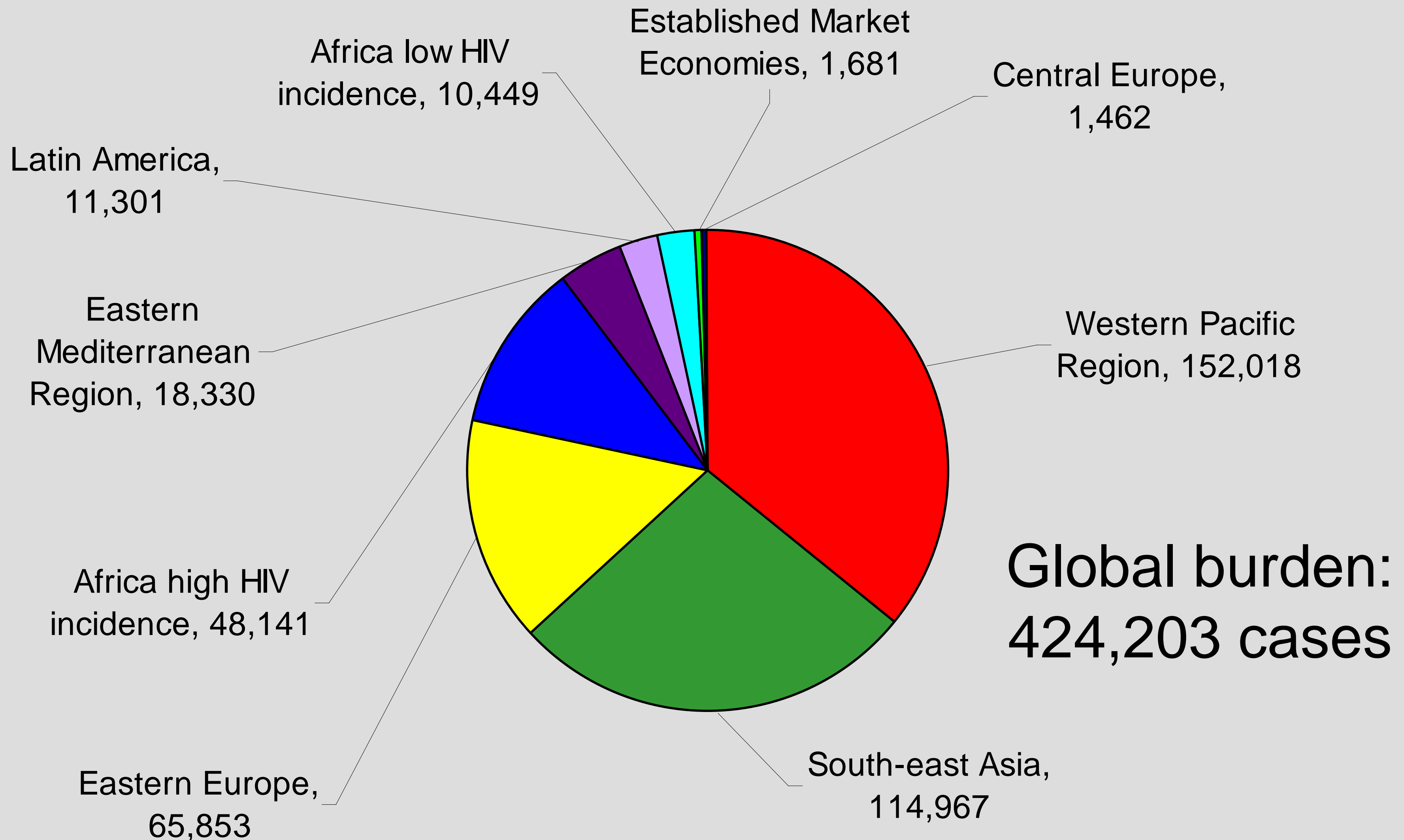
Cumulative DRS population coverage by WHO region - expected 2007



All MDR TB Cases by Regions



Global burden: 424,203 cases

Network contribution to TB control

- Strengthening TB laboratory services: still limited
  - focusing of activities: TB high-burden countries
    - Eastern Europe, Central Asia, Far East = OK
    - But hardly Africa
  - broadening the scope
    - AFB-microscopy network support
    - strengthening (and expansion?) of culture for diagnosis

DRS and Policy development
Phase 1: *1994-2002*

DRS findings (1st and 2nd report)

MDR-TB widespread, localized/severe epidemics, especially in FSU/China

Policy recommendations

Start of DOTS-Plus / GLC

Pilots expanding, evaluation of projects, increased access

DRS and Policy development
Phase 2: *2002 – present*

DRS findings (3rd report)

Must evaluate Cat II in some settings as well as Cat I in areas of high INH resistance prevalence, look at DRS and HIV

Policy recommendations

Treatment guidelines updated

DRS and Policy development

- Population based 1st line drug surveys important for trend analysis (reliable DST for H and R)
- Clear need to supplement population based DRS, with small cohort studies relevant for DOTS-Plus
    - Small surveys combined with history of treatment / antibiotic use to inform DOTS-Plus regimens
    - Obstacles: 2nd line DST much less reliable, lab capacity for 2nd line not developed locally (studies ongoing)

Challenges remaining

- Drug resistance testing
  - DST reliability and clinical significance
    - intermediate results? Techniques?
  - low- and middle income countries ?
    - relative priority of DRS versus AFB-microscopy
- Capacity building
  - in low-income : DST and/or microscopy ?

Challenges remaining

- Role in general TB research?
  - Not original objective
  - limited to some SRL
    - e.g. IUATLD clinical trials programme
  - extension on individual basis?