Antibiotic Resistant Gonorrhoea : Policy Consideration and Implication for Drug Development

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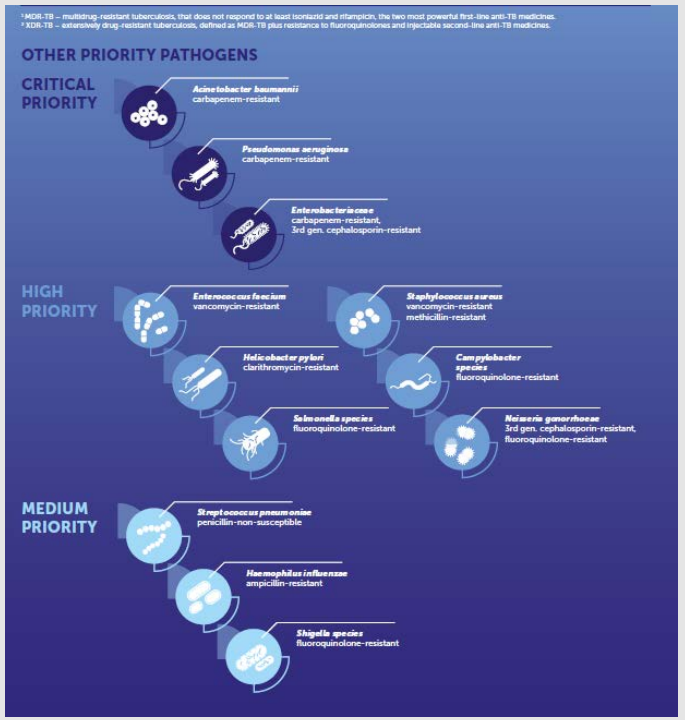
World Health Organization

Neisseria gonorrhoeae – high priority for R&D of new antibiotics



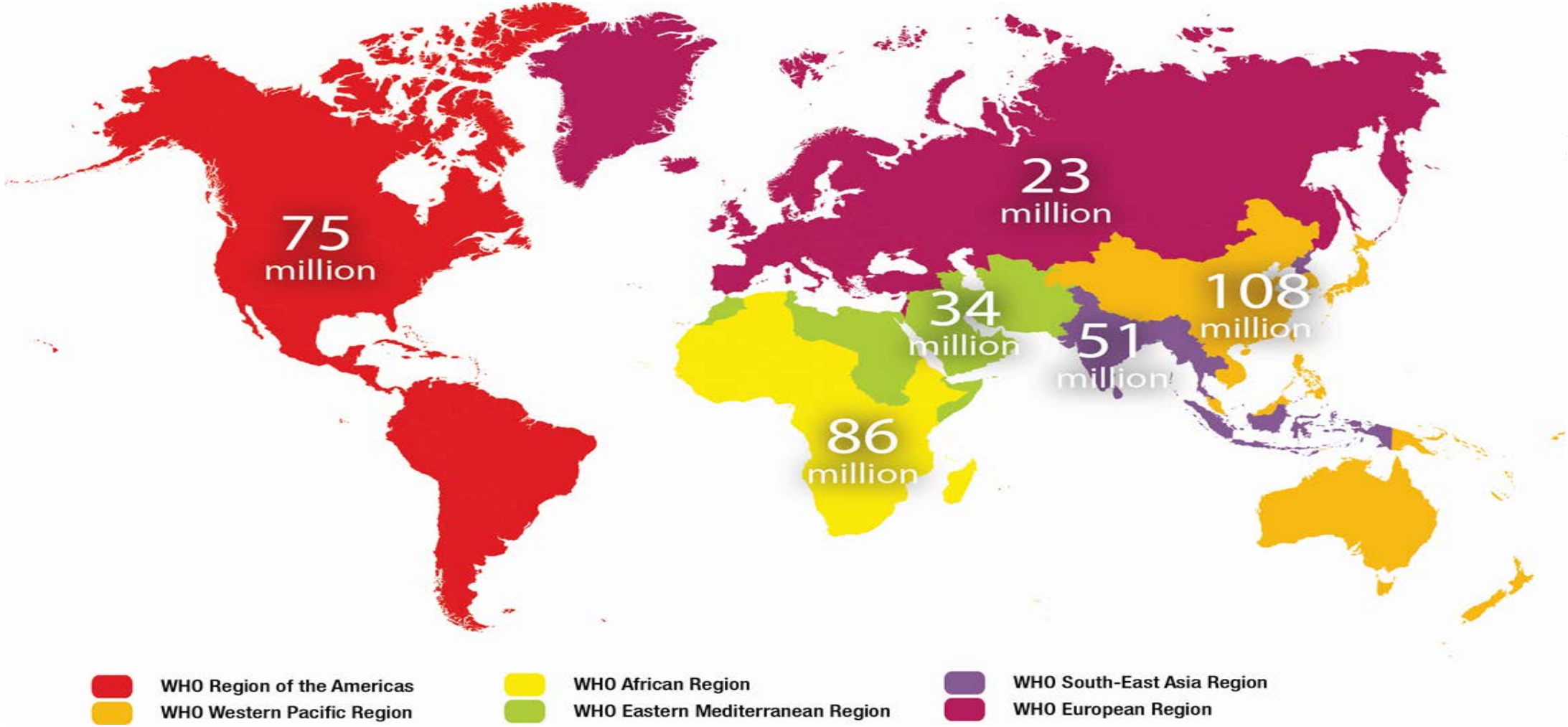
High community burden

- Common sexually transmitted infection : 78 million cases of gonorrhoea estimated globally in 2012
- Estimated 2012 global incidence of 19/1000 females and 24/1000 males
- Incidence is underestimates because of the lack of diagnostic capability in some parts of the world
- Resistance reported to all drugs recommended for empirical monotherapy
- Current recommended dual empirical treatment (fluroquinolone-free) does not guarantee clinical efficacy, will not entirely prevent the development of resistance and used in only a few parts of the world

Urgent threat for CDC and medium-high priority for PHAC

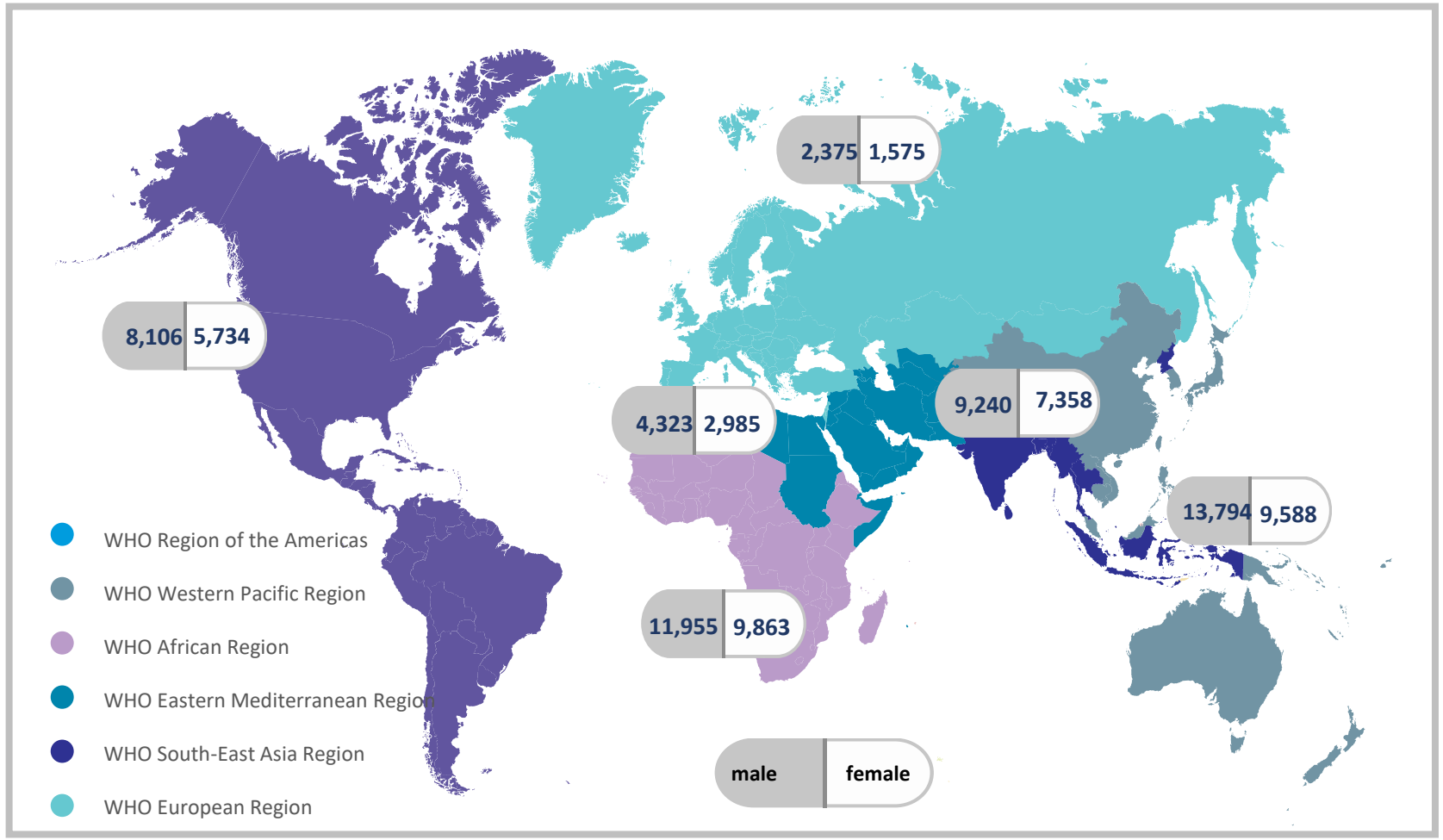
More than 1 million STIs acquired everyday

Estimated 376 million new cases of curable STIs in 2016 (chlamydia, gonorrhea, syphilis, trichomoniasis)



Rowley et al, https://www.who.int/bulletin/volumes/97/8/18-228486.pdf?ua=1

Estimated incident cases (‘000)* by WHO region, 2016
Gonorrhoea: 87 million new cases



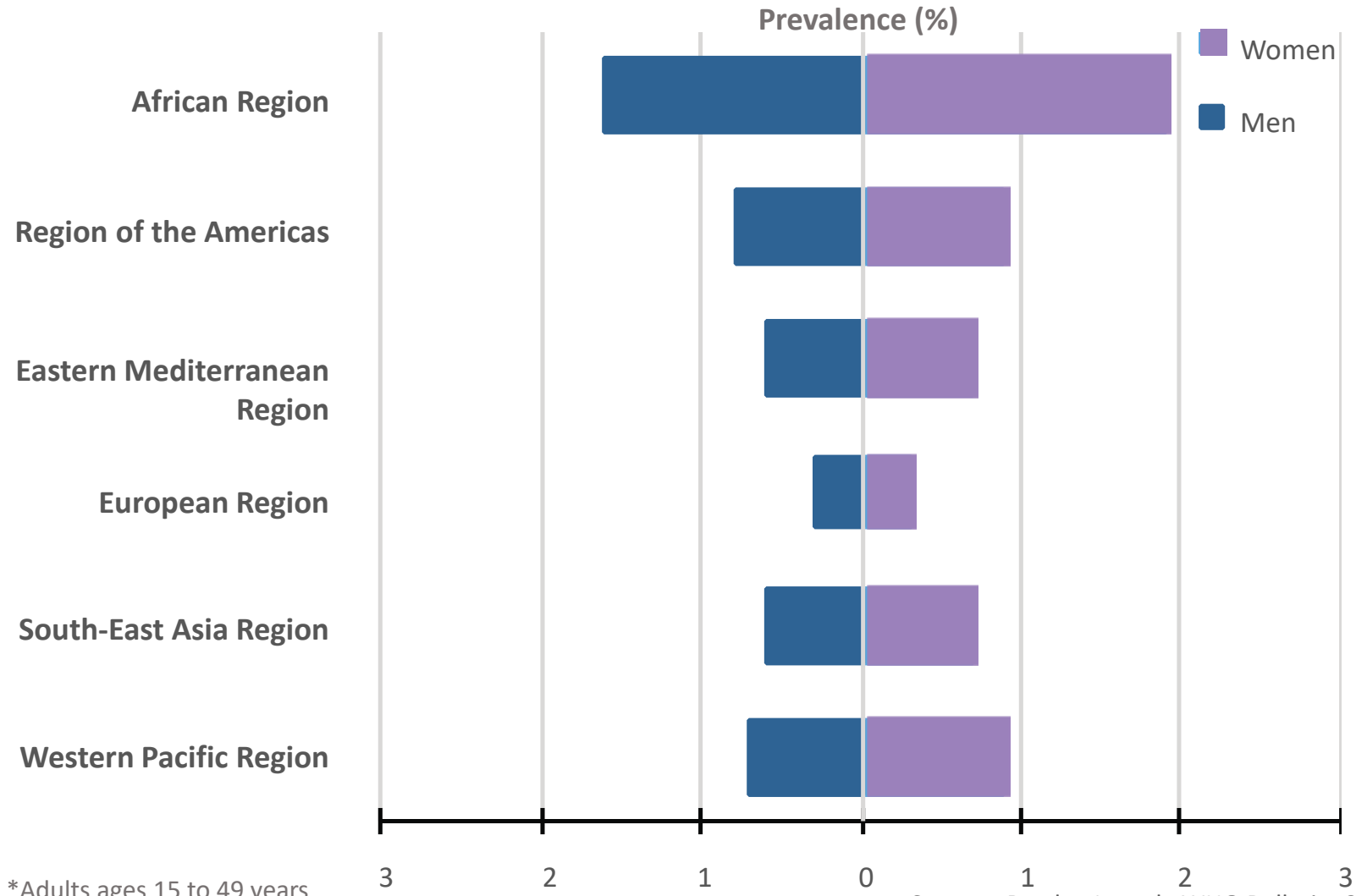
20/1000 in women

26/1000 in men

*Adults ages 15 to 49 years

Source: Rowley J, et al. WHO Bulletin, 2019

Estimated prevalence (%)* by WHO region
Gonorrhoea, 2016



0.9% women

0.7% men

*Adults ages 15 to 49 years

Source: Rowley J, et al. WHO Bulletin, 2019

'Worse than AIDS' - sex 'superbug' discovered in Japan called disaster in waiting

Published time: May 06, 2013 20:36
Edited time: May 08, 2013 09:41

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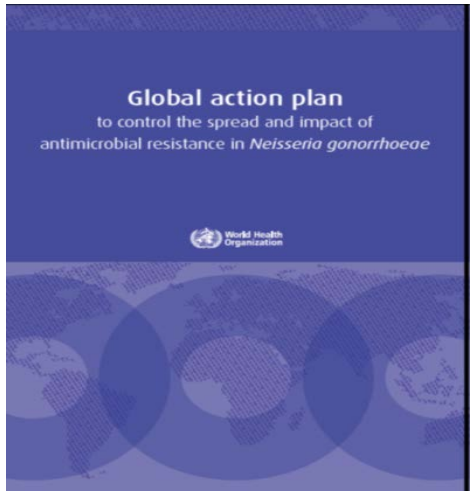
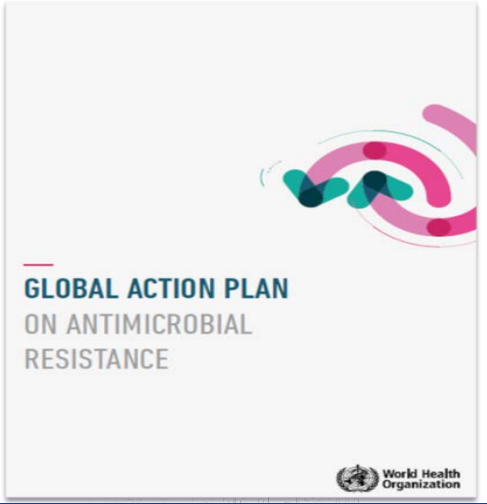
WHO Global Action Plans (KEY PRIORITIES)





Antimicrobial resistance in *Neisseria gonorrhoeae*: Global surveillance and a call for international collaborative action

PLOS Med. 2017

Teodora Wi[1]*, Monica M. Lahra[2,3], Francis Ndowa[4], Manju Bala[5], Jo-Anne R. Dillon[6], Pilar Ramon-Pardo[7], Sergey R. Eremin[8], Gail Bolan[9], Magnus Unemo[10]

Sexual Health, 2019, **16**, 412–425
https://doi.org/10.1071/SH19023

Review

World Health Organization Global Gonococcal Antimicrobial Surveillance Program (WHO GASP): review of new data and evidence to inform international collaborative actions and research efforts

Magnus Unemo[A,K], Monica M. Lahra[B], Michelle Cole[C], Patricia Galarza[D], Francis Ndowa[E], Irene Martin[F], Jo-Anne R. Dillon[G], Pilar Ramon-Pardo[H], Gail Bolan[I] and Teodora Wi[J]

Countries with reported decreased susceptibility/resistance (DS/R) to ceftriaxone in *N. gonorrhoeae*, WHO GASP/GLASS 2015-16 vs. 2017-18

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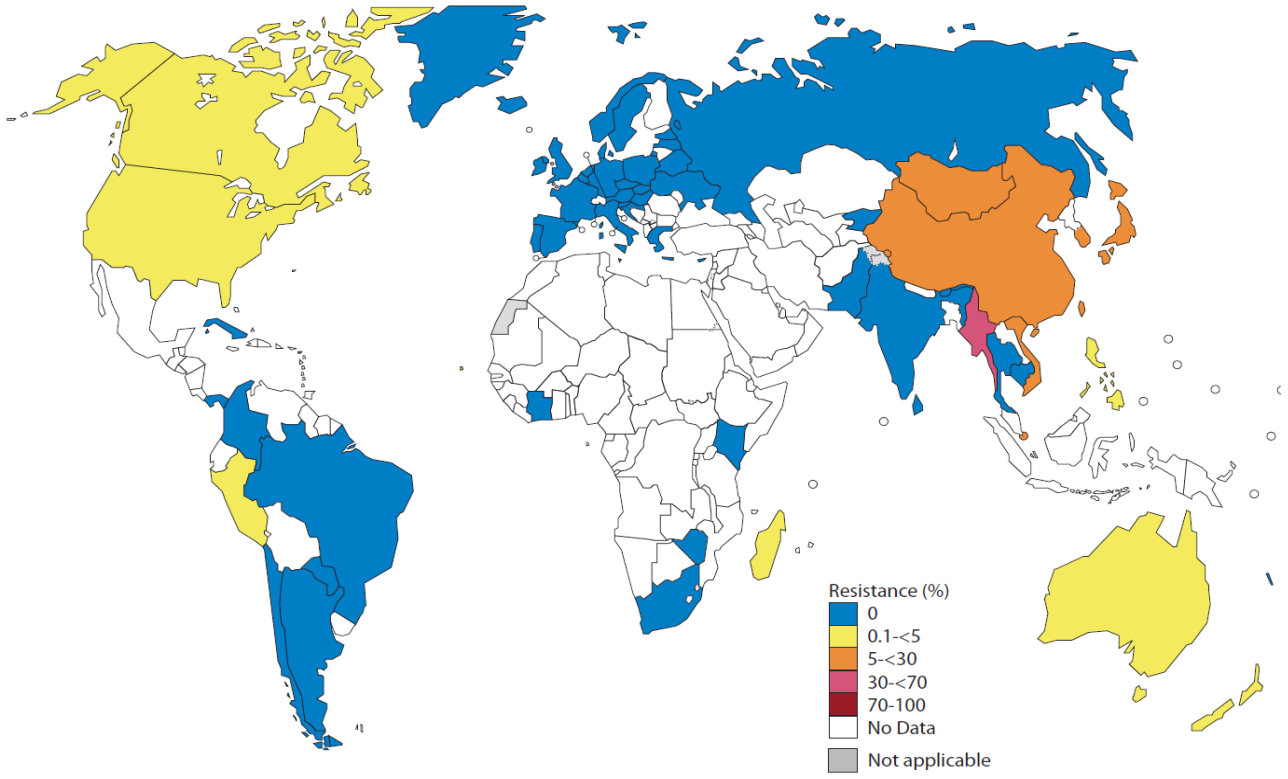
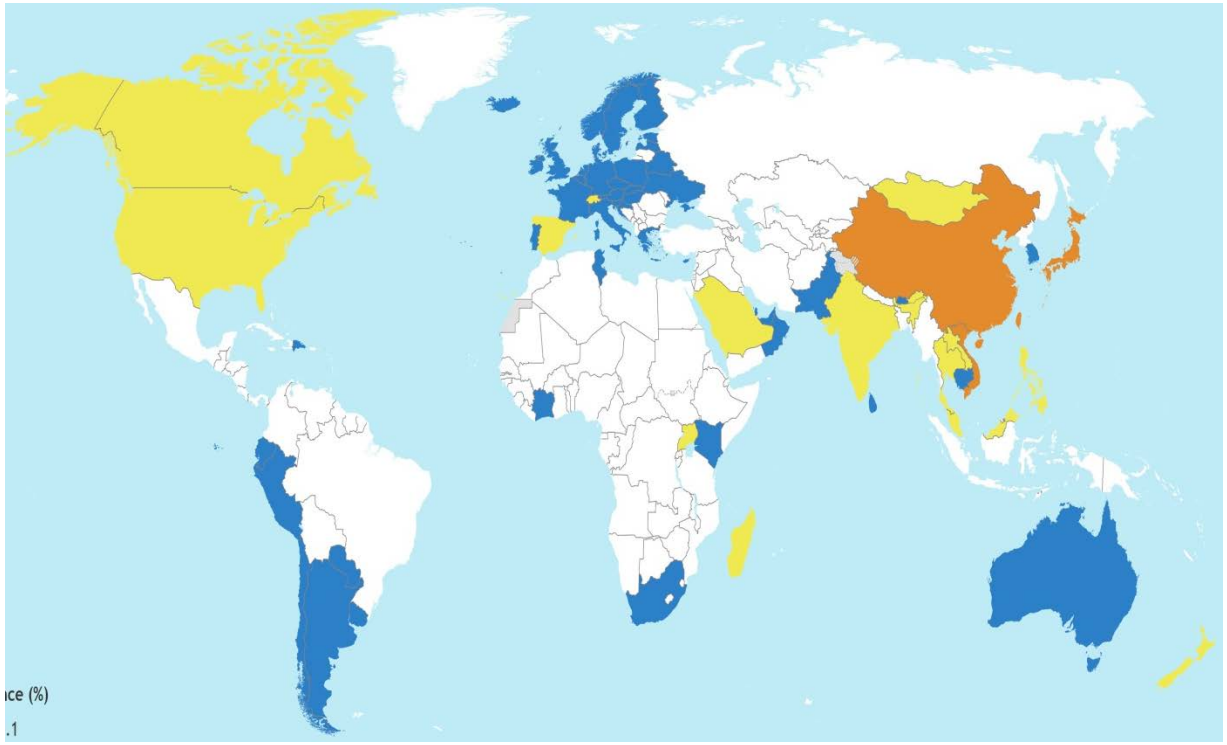
23.8% of countries
(11.1% of countries ≥5%)



Unemo et al. Sex Health. 2019

30.8% of countries
(8.8% of countries ≥5%)

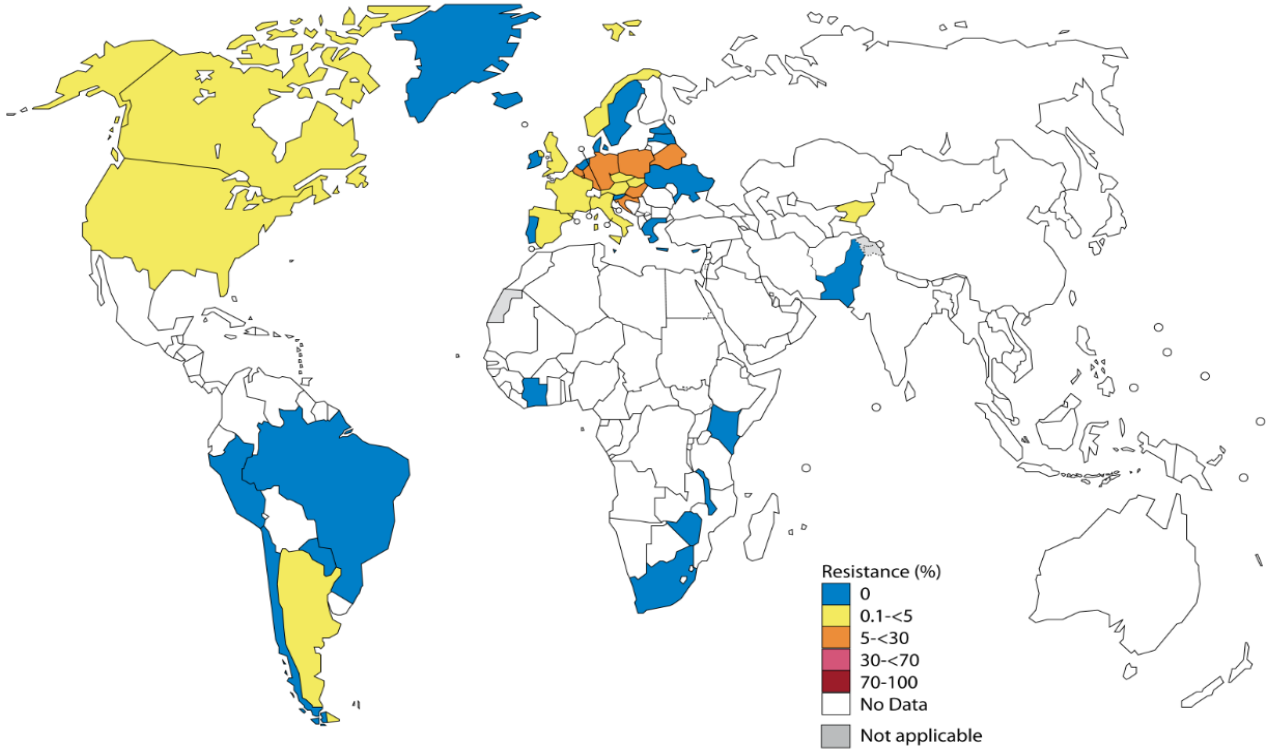


Unemo et al. In review

Countries with reported decreased susceptibility/resistance (DS/R) to cefixime in *N. gonorrhoeae*, WHO GASP/GLASS 2015-16 vs. 2017-18

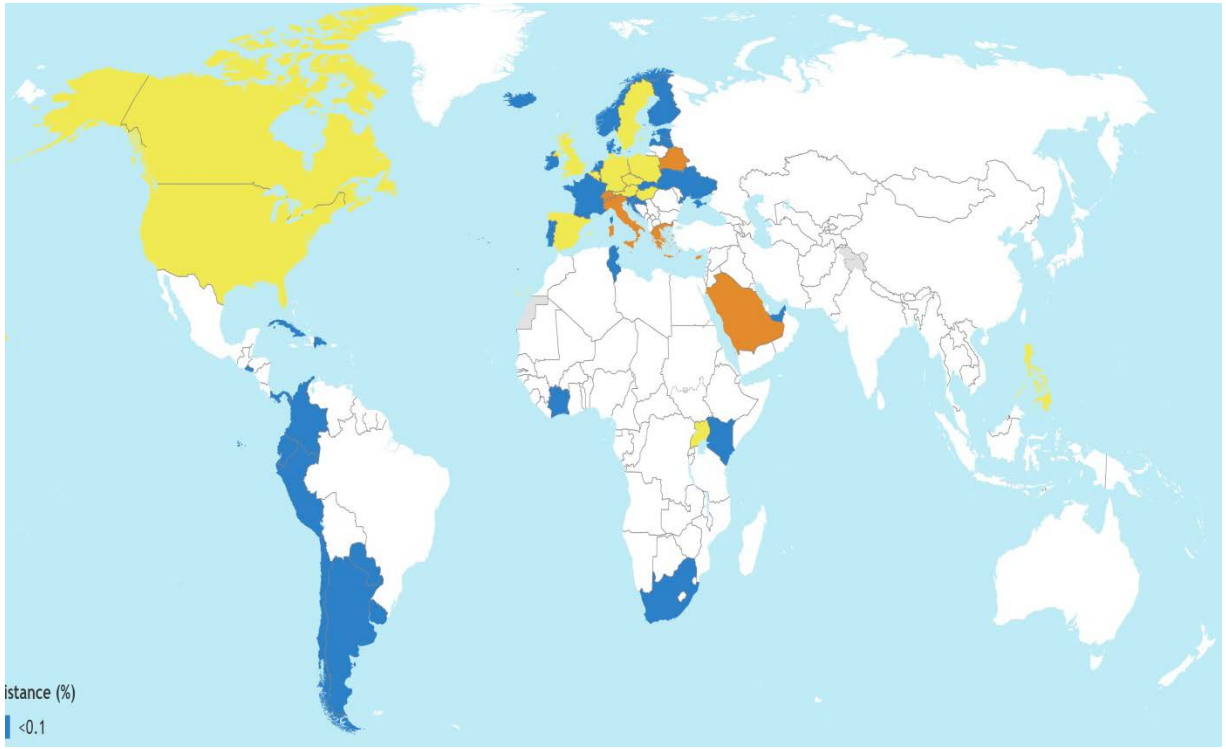
World Health Organization

45.2% of countries
(16.7% of countries ≥5%)



Unemo et al. Sex Health. 2019

41.7% of countries
(17.6% of countries ≥5%)

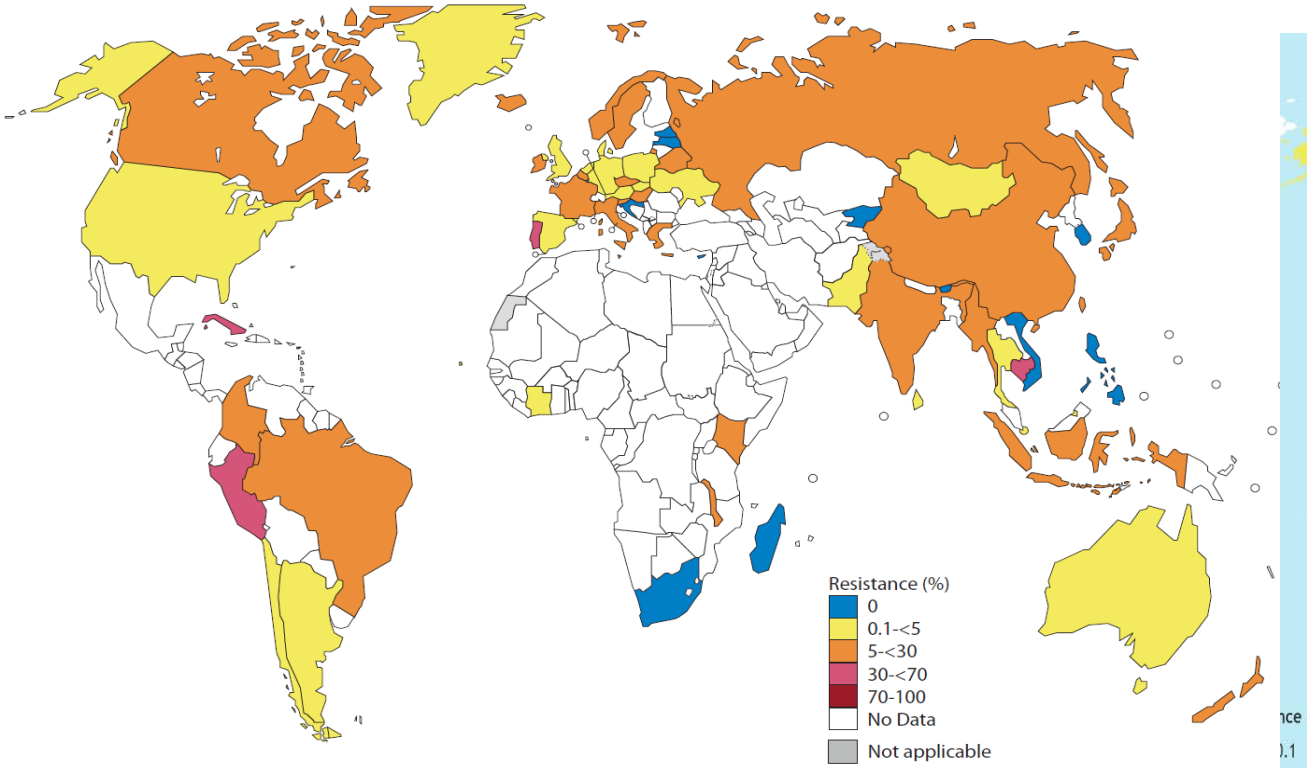


Unemo et al. In review

Countries with reported resistance to azithromycin in *N. gonorrhoeae*, WHO GASP/GLASS 2015-16 vs. 2017-18

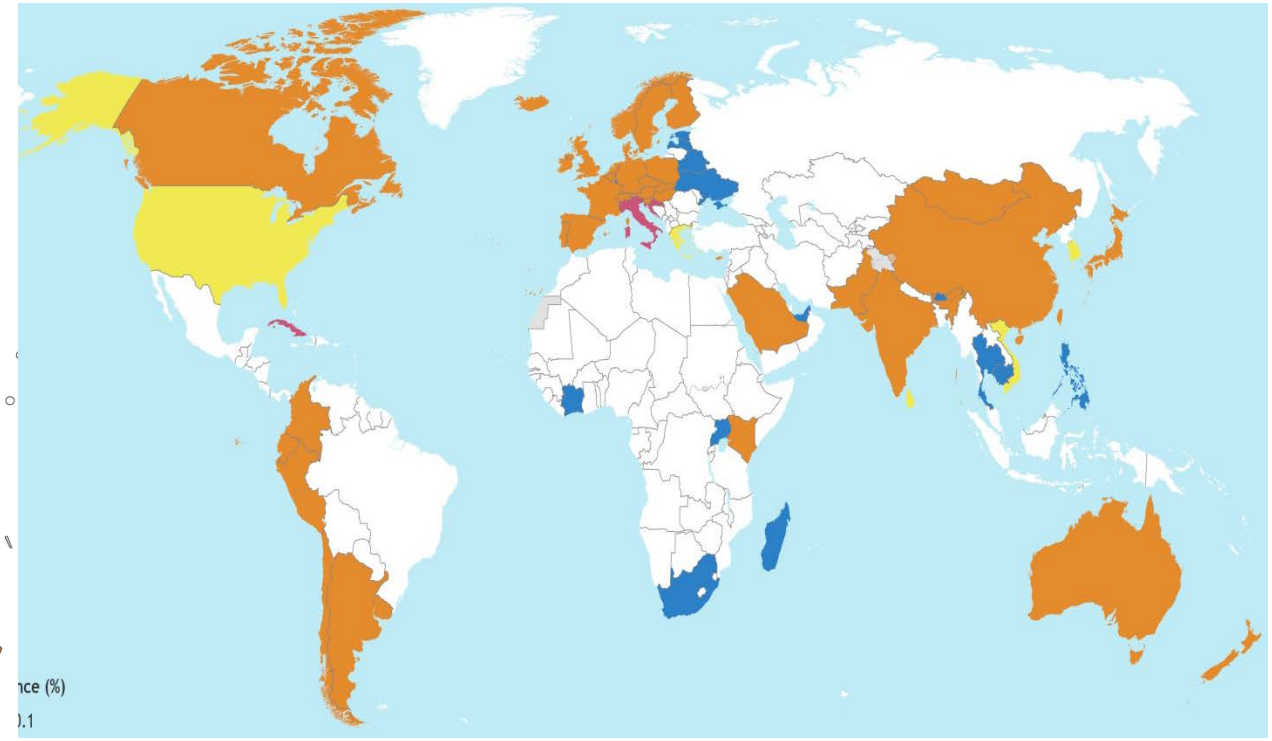
World Health Organization

80.6% of countries
(48.4% of countries ≥5%)



Unemo et al. Sex Health. 2019

83.6% of countries
(72.1% of countries ≥5%)

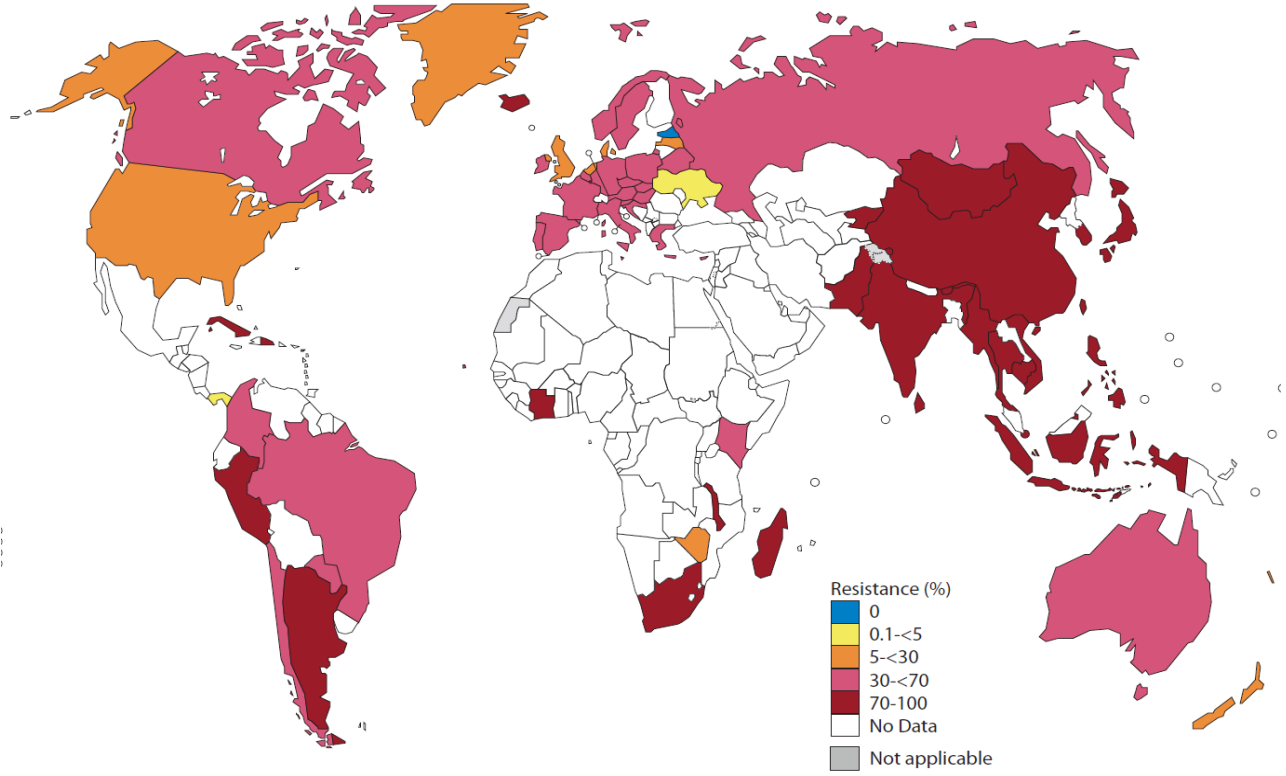


Unemo et al. In review

Countries with reported resistance to ciprofloxacin in *N. gonorrhoeae*, WHO GASP/GLASS 2015-16 vs. 2017-18

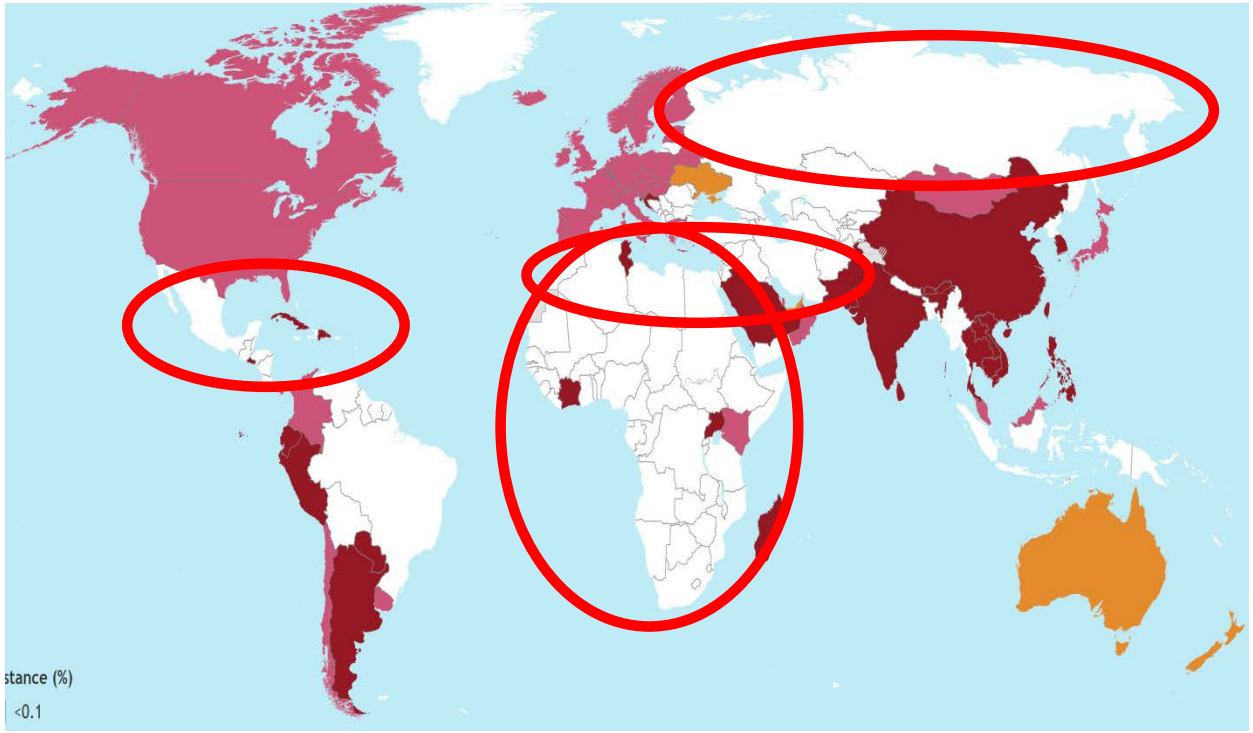
World Health Organization

100% of countries
(17.9% of countries ≥90%)
(97.0% of countries ≥5%)



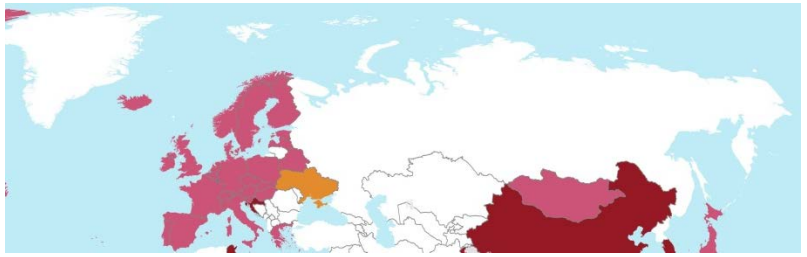
Unemo et al. Sex Health. 2019

100% of countries
(22.9% of countries ≥90%)
(100% of countries ≥5%)

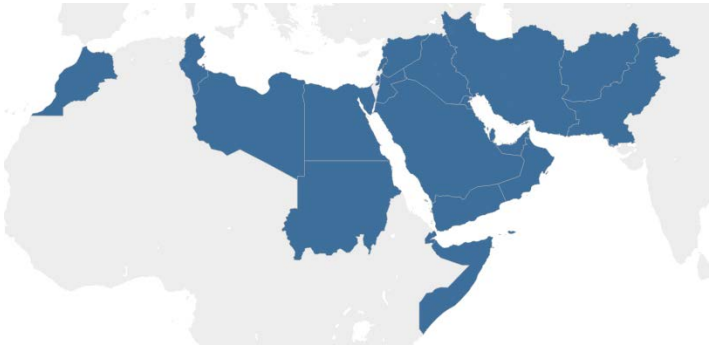


Unemo et al. In review

Expansion crucial especially in non-EU/EEA WHO EUR, EMR and AFR countries



Non-EU/EEA countries of WHO European Region (11.5% of countries; mostly former Soviet Republics)

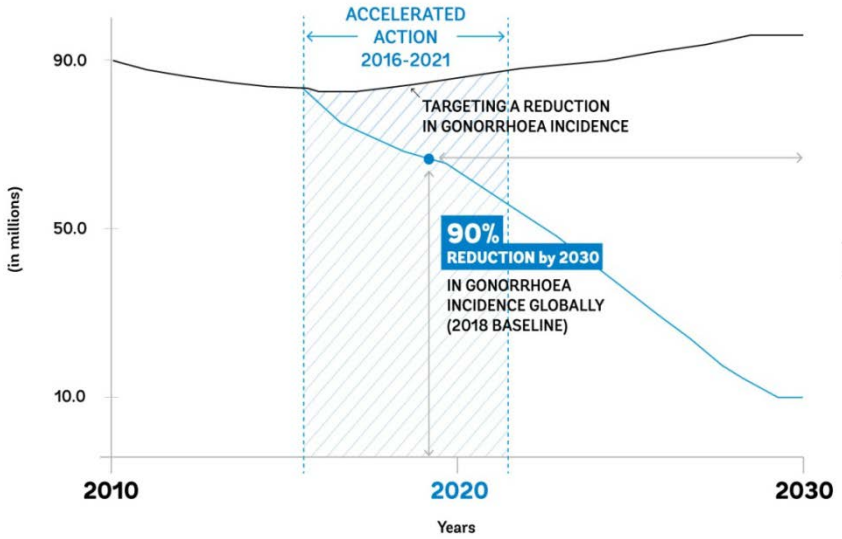


WHO Eastern Mediterranean Region (31.8% of countries, but <200 isolates totally per year)

WHO African Region (10.6% of countries)

Ambitious goals for ending STI as public health threat by 2030

World Health Organization



Three priority areas:

***Gonorrhoea* – risk of resistance and untreatable gonorrhoea**

Syphilis - elimination of congenital syphilis

Human papillomavirus (HPV) – vaccination

Incidence and Prevention:

- 90% reduction of *T. pallidum* incidence
- **90% reduction in *N. gonorrhoeae* incidence**
- ≤50 cases of congenital syphilis per 100 000 live births in 80% of countries;
- 80% human papillomavirus (HPV) vaccine coverage in adolescent 9-14years of age in 80% of countries.

Link: http://www.who.int/reproductivehealth/publications/rtis/ghss-stis/en/

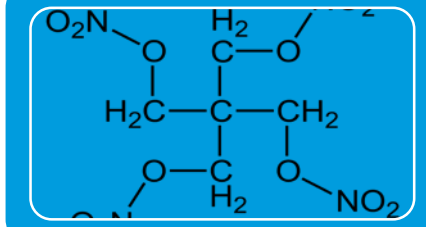
Global Action Plan to Control the Spread and Impact of AMR in *Neisseria gonorrhoeae*

World Health Organization

- Gonorrhoea Antimicrobial Surveillance to inform treatment guidelines and policy
- STI Prevention and Control
- Development of new gonorrhoea treatment
- Antibiotic Stewardship: POCT for gonorrhoea ID & AMR detection
- Facilitate gonorrhoea vaccine development

Multi-drug resistant gonorrhoea: R&D Roadmap GARDP/WHO

World Health Organization



Accelerate the development of new chemical entity

Evaluate the potential of existing antibiotics and their combinations

Explore co-packaging and development of fixed-dose combinations

Support the development of simplified treatment guidelines and foster conservation

Target product profile for therapy of diagnosed uncomplicated gonorrhoea

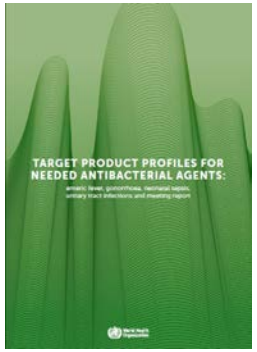
World Health Organization

	Minimal TPP	Preferred TPP
Indication for use	Treatment of suspected or diagnosed uncomplicated urogenital gonorrhoea	Treatment of diagnosed uncomplicated urogenital gonorrhoea and extra-genital gonorrhoea (anorectal and oropharyngeal)
Target population	Adults and adolescents in areas with resistance to the current recommended first-line treatment.	Adults and adolescents in areas with resistance to the current recommended first-line treatment
Access and affordability	• Commit to an **access and stewardship strategy** that promotes availability at fair prices. • **Fair price**: affordable for health systems and patients, but at the same time provides sufficient market incentive for industry to invest in innovation and the production of quality essential health products • Governments need to commit to ensure **availability and affordability of essential new antibiotic treatments**. In particular for reserve antibiotics, governments should explore models where procurement and reimbursement are linked to **availability instead of volume to foster appropriate use** • Stewardship and appropriate use are essential to preserve the effectiveness of any new antibacterial treatment. Developers should not register the product for use in animals or plants or develop a treatment of the same class for use in animals or plants. • Access and stewardship plan should be based on **ethical promotion and distribution**. • Manufacturing should be in line with **best industry practices** in the management of emissions to the environment to minimize the risks of spreading antimicrobial resistance (AMR).	

Target product profile for therapy of diagnosed uncomplicated gonorrhoea

World Health Organization

	Minimal TPP	Preferred TPP
Safety/tolerability	No patient monitoring required post treatment. For oral route, low frequency of side effects, including nausea and vomiting (comparable to current treatment). For IM use, good local tolerance.	No patient monitoring required post treatment. For oral route, low frequency of side effects, including nausea and vomiting (comparable to current treatment). For IM use, good local tolerance. Acceptable for use in pregnancy and lactation based on nonclinical studies.
In vitro activity	In vitro activity against *N. gonorrhoeae* resistant to extended-spectrum cephalosporins and macrolides, no cross resistance to any other known antibiotic class (best achieved by a new class and/or new target and/or new mode of action). Activity measured by minimum inhibitory concentration (MIC) and dynamic in vitro models that account for protein binding, intracellular penetration and activity against intracellular bacteria. Low potential for emergence of mutational resistance.	
Clinical efficacy	Non-inferiority in clinical trials versus current standard of care, as in US Food and Drug Administration (FDA) guidance, for urogenital gonorrhoea.	Non-inferiority to current standard of care (as in FDA guidance) for urogenital gonorrhoea, and equivalent to current care for extra-genital gonorrhoea.



Target product profile for therapy of diagnosed uncomplicated gonorrhoea

World Health Organization

	Minimal TPP	Preferred TPP
Dose regimen	1–3 doses, up to 3 days Single dose preferred at least for urogenital gonorrhoea	Single dose preferred at least for urogenital gonorrhoea; but 1–3 doses, up to 3 days, acceptable to treat extra-genital gonorrhoea.
Route of administration	Oral or IM	Oral or IM
Product stability and storage	Heat stable, 3-year shelf-life in hot tropic/ humid climate (simulated with 30°C and 65% relative humidity).	Heat stable, 3-year shelf-life in hot tropic/ humid climate (simulated with 30°C and 65% relative humidity).
Pharmacokinetics	Pharmacokinetic data available to support use in acute infection.	Pharmacokinetic data available to support use in acute infection and elimination of colonizing extragenital bacteria and show intracellular activity.
Drug interactions	Minimal relevant DDIs, including HIV medicines and other STI treatments.	No relevant DDIs, including HIV medicines and other STI treatments.

Formulate question

Select outcomes

Rate importance

P
I
C
O

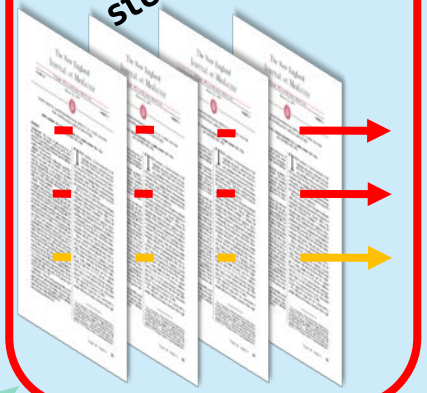
Outcome — Critical

Outcome — Critical

Outcome — Important

Outcome — Not important

Outcomes across studies



Create evidence profile with GRADEpro

Rate quality of evidence for each outcome

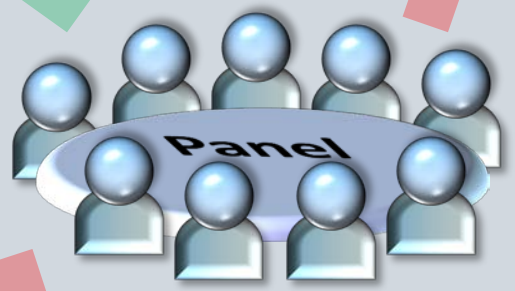
High	⊕⊕⊕⊕
Moderate	⊕⊕⊕O
Low	⊕⊕OO
Very low	⊕OOO

World Health Organization

Systematic review

Recommendation

Input?



Grade overall quality of evidence
across outcomes based on lowest quality of ***critical*** outcomes

Grade recommendations
- For or against (direction) ↓↑
- Strong or conditional/weak (strength

By considering balance of:
- ❑ Quality of evidence
- ❑ Balance benefits/harms
- ❑ Values and preferences
- ❑ Resource cost
- ❑ Cost effectiveness
- ❑ Feasibility
- ❑ Acceptability
- ❑ Equity

Guideline

Formulate Recommendations (↓↑ | ⊕...)
- "The panel recommends that ....should..."
- "The panel suggests that ....should..."
- "The panel suggests to **not** ..."
- "The panel recommends to **not**..."

Quality of Evidence (GRADE approach)

Study design	Initial confidence in an estimate of effect
Randomized controlled trials	High confidence
Observational studies	Low confidence

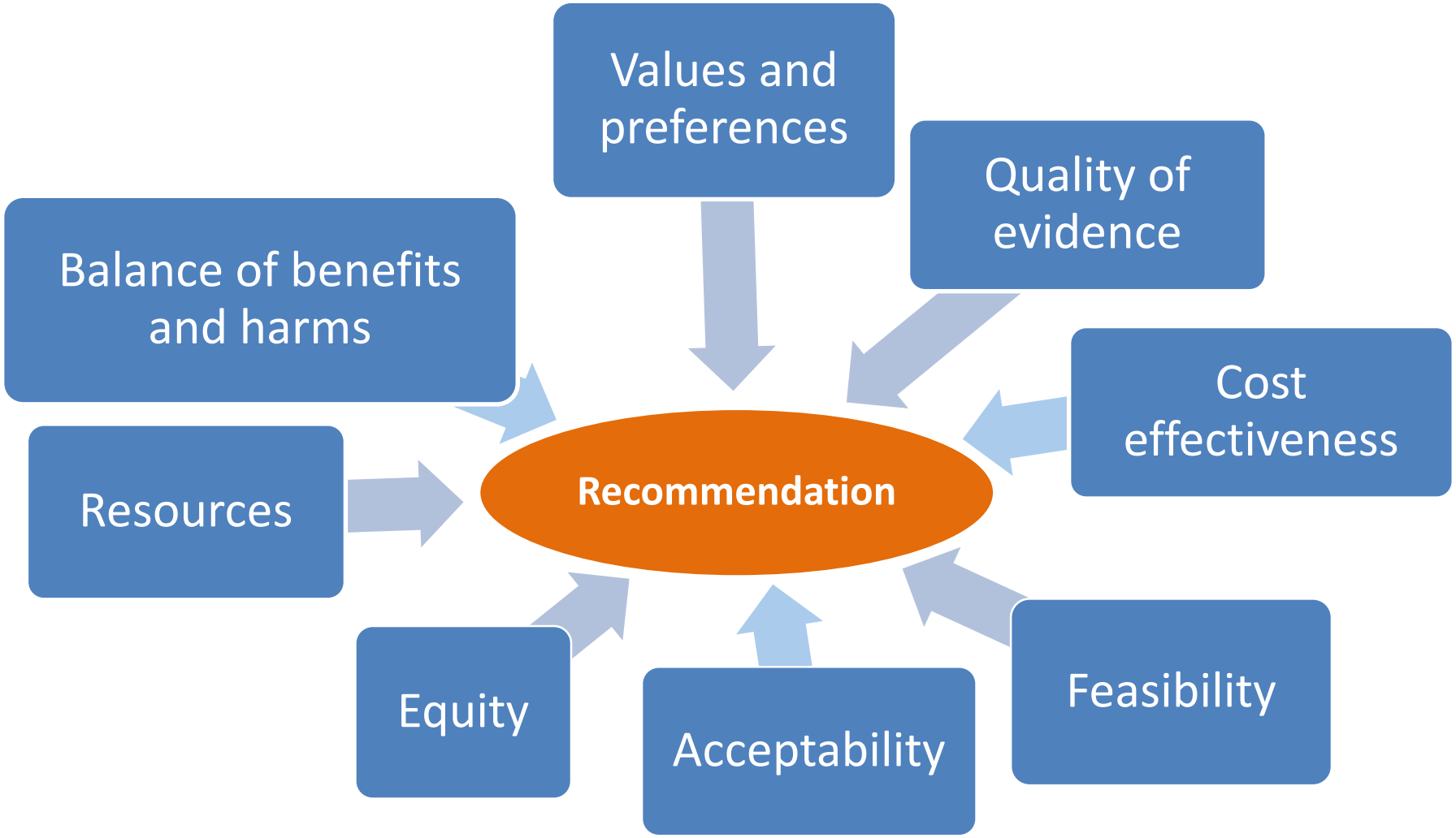
Reason for considering lowering or raising confidence	
Lower if	Higher if
Risk of bias Inconsistency Indirectness Impression Publication bias	Large effect Dose Response All plausible confounding and bias - Would reduce a demonstrated effect or - Would suggest a spurious effect if no effect was observed

Confidence in an estimate of effect across all considerations
High ⊕⊕⊕⊕
Moderate ⊕⊕⊕O
Low ⊕⊕OO
Very low ⊕OOO

Clinical trial design consideration to support the development of the gonorrhoea guidelines

- Randomized control trials (preferred source of evidence)
  - Random sequence generation
  - Concealment of allocation to treatment group
  - Blinding of participants and investigators
  - Reporting of data on all study participants – attrition and exclusion from analysis
  - Complete reporting of all study outcomes
- Population: include men, women, key population (MSM and FSW), HIV positive
- Intervention (drug – dosage (anatomic sites) / Comparator (standard of care)
- Critical Outcomes
  - Often available: microbiological cure, clinical cure and side effects
  - Limited data: compliance, complication, transmission to partners, quality of life
- Antimicrobial resistance monitoring including treatment failure

Factors that determine the direction and strength of a recommendation – additional data needed



GRADE

Drug development and Antimicrobial Stewardship

World Health Organization

Implementation of coordinated interventions and prevent development of resistance

- Promote drug development
- Access to new antibiotics – positioning, market assessment, EML
- Appropriate antibiotic use - low cost point of care test