

The serious threat of multidrug-resistant and untreatable gonorrhoea: the pressing need for global action to control the spread of antimicrobial resistance, and mitigate the impact on sexual and reproductive health



EDITOR'S
CHOICE

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STIs remain a major cause of morbidity and mortality worldwide. The WHO estimated that >498 million new cases of syphilis, gonorrhoea, chlamydial infection and trichomoniasis occurred globally in 2008 in adults (15–49 years of age). More than 106 million were gonococcal infections.¹ Accordingly, gonorrhoea remains a major global public health problem with serious health, social and economic consequences. Inadequate control and treatment can result in severe complications, such as pelvic inflammatory disease, leading to infertility or ectopic pregnancy, and neonatal eye infections which can cause blindness. Up to 10% of women who remain untreated (or inadequately treated) for chlamydial and gonococcal infections may become infertile. Urogenital gonorrhoea is also asymptomatic in at least 50% of women, which leaves the infections undetected and untreated with the risk of severe complications. On a global scale, up to 4000 newborn babies, annually, may become

blind because of gonococcal and chlamydial ophthalmia neonatorum.² In men, gonococcal infections cause symptomatic urethritis which, if untreated, can result in epididymitis in 10%–30% of cases,^{w1} that may lead to infertility. Gonorrhoea also significantly enhances the transmission of HIV. The burden of gonococcal infections is highest in countries that are least able to manage them because of several factors, including stigma, inadequate resources and lack of appropriate diagnostics, surveillance and antimicrobial treatment. The problem is further compounded by the ability of *Neisseria gonorrhoeae* to develop antimicrobial resistance (AMR) within a relatively short time span.^{3 w2 w3}

Historically, since the advent of the antibiotic era, gonococcal infections have been easy to treat. However, the susceptibility of *N gonorrhoeae* to sulphonamides and penicillins from the mid-1930s and mid-1940s, respectively, gradually eroded as the organism developed a number of mechanisms for antimicrobial resistance. The mid-1980s and early 1990s were promising with the introduction of effective single-dose treatments that could be administered orally, such as fluoroquinolones (mainly ciprofloxacin and ofloxacin) and oral third-generation cephalosporins (cefixime being the most potent one). The macrolide azithromycin was even more exciting as it could treat both gonococcal and chlamydial infections with a single oral dose regimen. However, resistance to fluoroquinolones emerged only after about a decade, and these

were abandoned as first-line empiric treatment for gonorrhoea in the Asia-Pacific region already in the mid-to-late 1990s and, subsequently, in the USA, Europe and parts of Africa.^{3 w2 w3–w6} Azithromycin-resistant *N gonorrhoeae* emerged in the mid-to-late 1990s,^{4 w7} and, subsequently, also high-level azithromycin resistance has been described from several countries.^{5 w8–w11} Thus, since the early 2000s, third-generation cephalosporins (mainly cefixime and ceftriaxone) have been the sole class of antimicrobials recommended as first-line empiric treatment.^{3 w2 w3}

Worryingly, resistance and treatment failures to cefixime have been verified in Japan⁶ and recently in Europe.^{7–9} The recent report of a strain of *N gonorrhoeae* in Japan that was highly resistant to the parenteral ceftriaxone, and associated with a probable treatment failure with ceftriaxone,¹⁰ the last remaining option for empiric treatment, sounded alarm bells of significant future challenges to the treatment and control of gonococcal infections and their complications. This was also followed by the identification of a highly ceftriaxone-resistant strain in France¹¹ and in Spain.¹² Furthermore, many regions, worldwide, describe a decreasing susceptibility to ceftriaxone, and reports of ceftriaxone treatment failure of gonococcal pharyngeal infections have been published.^{3 13 w2 w3} Given the ability of *N gonorrhoeae* to develop AMR within a relatively short time span compounded with its ability to retain the resistance to previous antibiotics, even after their use has been discontinued, the threat of a widespread ceftriaxone resistance and untreatable gonorrhoea in certain circumstances is real.^{3 10 11 w2 w3}

The global trend of AMR in *N gonorrhoeae*, and decreased susceptibility and resistance to the third-generation cephalosporins, in the age of easy international travel dictated that a global approach needed to be elaborated to respond to the emerging menace of untreatable gonorrhoea. This was especially important because gonococcal AMR data were not available in many settings, and the true global magnitude of the problem is unknown. Therefore, the WHO Global Gonococcal Antimicrobial Surveillance Programme (WHO Global GASP), initially established in the 1990s, was revisited and revamped in 2009 as a network of collaborators in order to enable a global, coordinated response. The WHO Global GASP network consists of the WHO Headquarters, Geneva, as the managing focal centre working with interregional collaborators in Africa, Asia, the Americas, Europe and the

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Western Pacific, and aims to encourage and recruit national laboratories to monitor gonococcal AMR data, with particular attention to third-generation cephalosporins, and identify treatment failures using recommended treatment.

To facilitate the functioning of the GASP network and engage the support of governments and the international community and donors in this venture, the WHO published the 'Global Action Plan to Control the Spread and Impact of Antimicrobial Resistance in *N gonorrhoeae*' in June 2012.¹⁴ The Global Action Plan aims to facilitate early detection of strains resistant to recommended treatment, combined with a public health response to mitigate the impact of cephalosporin-resistant *N gonorrhoeae* on sexual and reproductive health morbidity. The WHO Global Action Plan calls for the public health approach to the control of gonococcal infections and the emergence of multidrug-resistant and untreatable gonorrhoea. Some of the main components and actions of the Global Action Plan are:

- ▶ Advocacy for increased awareness on correct use of antibiotics among healthcare providers and the consumers, particularly in key populations, including men-who-have-sex-with-men and sex workers.
- ▶ Effective prevention, diagnosis and control of gonorrhoea, using prevention messages, interventions, recommended diagnosis and treatment regimens.
- ▶ Systematic monitoring and early detection of treatment failures with recommended treatment (cefixime and ceftriaxone) by developing a standard case definition of treatment failure, and protocols for verification, reporting and management of failure.
- ▶ Effective drug regulations and prescription policies.
- ▶ Strengthened AMR surveillance, especially in countries with a high burden of gonococcal infections (and/or gonococcal AMR), other STIs and HIV.
- ▶ Capacity building to establish regional networks of laboratories to perform quality-assured gonococcal culture and antimicrobial susceptibility testing.
- ▶ Research to identify new molecular methods for detecting and monitoring antimicrobial resistance.
- ▶ Research (basic science, in vitro and clinical studies) to identify alternative

effective treatment strategies and/or antimicrobials (or other effective compounds) for gonorrhoea.

This Global Action Plan will be implemented within the WHO's 'Global Strategy for the prevention and control of sexually transmitted infections: 2006–2015' which was adopted by the WHO Member States at the 59th World Health Assembly in May 2006.² To ensure harmonisation and sustainability, the WHO GASP network will be linked to, and operate within, the WHO Policy Package to Combat AMR which was launched on World Health Day 2011 in Geneva.¹⁵

The implementation of the WHO GASP activities both at the global and national levels can only be achieved with the formation of partnerships for funding and training among different but related programmes, and adequate funding for surveillance of STIs, in general, and quality-assured gonococcal AMR testing, in particular. Several region-specific and even country-specific action plans to control the spread of gonococcal antimicrobial resistance, are also under preparation, these plans are also crucial for the global response to the serious threat of untreatable gonorrhoea. Ultimately, it is essential to identify new strategies and/or antimicrobials (or other effective compounds) for effective treatment of gonorrhoea. It is imperative that this research is adequately supported and funded by national and international partners.

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▶ Additional references are published online only. To view these references please visit the journal online (<http://sti.bmj.com/content/88/5.toc>).

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REFERENCES

1. **World Health Organization.** *Global Prevalence and Incidence Of Selected Curable Sexually Transmitted*

Infections—2008: Overview and Estimates. Geneva, 2012. http://www.who.int/reproductivehealth/publications/rtis/2008_STI_estimates.pdf (accessed 6 Jul 2012).

2. **World Health Organization.** *Global Strategy For The Prevention And Control of Sexually Transmitted Infections: 2006–2015.* Geneva, 2007. ISBN: 978 92 4 156347 5. <http://www.who.int/reproductivehealth/publications/rtis/9789241563475> (accessed 28 May 2012).

3. **Tapsall JW, Ndowa F, Lewis DA, et al.** Meeting the public health challenge of multidrug- and extensively drug-resistant *Neisseria gonorrhoeae*. *Expert Rev Anti Infect Ther* 2009;**7**:821–34.

4. **Dillon JA, Ruben M, Li H, et al.** Challenges in the control of gonorrhoea in South America and the Caribbean: monitoring the development of resistance to antibiotics. *Sex Transm Dis* 2006;**33**:87–95.

5. **Palmer HM, Young H, Winter A, et al.** Emergence and spread of azithromycin-resistant *Neisseria gonorrhoeae* in Scotland. *J Antimicrob Chemother* 2008;**62**:490–4.

6. **Yokoi S, Deguchi T, Ozawa T, et al.** Threat to cefixime treatment of gonorrhoea. *Emerg Infect Dis* 2007;**13**:1275–7.

7. **Ison CA, Hussey J, Sankar KN, et al.** Gonorrhoea treatment failures to cefixime and azithromycin in England, 2010. *Euro Surveill* 2011;**16**:19833.

8. **Unemo M, Golparian D, Syversen G, et al.** Two cases of verified clinical failures using internationally recommended first-line cefixime for gonorrhoea treatment, Norway, 2010. *Euro Surveill* 2010;**15**:19721.

9. **Unemo M, Golparian D, Stary A, et al.** First *Neisseria gonorrhoeae* strain with resistance to cefixime causing gonorrhoea treatment failure in Austria, 2011. *Euro Surveill* 2011;**16**:19998.

10. **Ohnishi M, Golparian D, Shimuta K, et al.** Is *Neisseria gonorrhoeae* initiating a future era of untreatable gonorrhoea? Detailed characterization of the first strain with high-level resistance to ceftriaxone. *Antimicrob Agents Chemother* 2011;**55**:3538–45.

11. **Unemo M, Golparian D, Nicholas R, et al.** High-level cefixime- and ceftriaxone-resistant *N gonorrhoeae* in France: novel penA mosaic allele in a successful international clone causes treatment failure. *Antimicrob Agents Chemother* 2012;**56**:1273–80.

12. **Cámara J, Serra J, Ayats J, et al.** Molecular characterization of two high-level ceftriaxone-resistant *Neisseria gonorrhoeae* isolates detected in Catalonia, Spain. *J Antimicrob Chemother.* Published Online First: 7 May 2012. doi:10.1093/jac/dks162

13. **Unemo M, Golparian D, Hestner A.** Ceftriaxone treatment failure of pharyngeal gonorrhoea verified by international recommendations, Sweden, July 2010. *Euro Surveill* 2011;**16**:19792.

14. **World health Organization.** Global action plan to control the spread and impact of antimicrobial resistance in *Neisseria gonorrhoeae*. 2012. ISBN: 978 92 4 150350 1. <http://www.who.int/reproductivehealth/publications/rtis/9789241503501> (accessed 28 May 2012).

15. **World Health Day.** *Policy Briefs/WHO Policy Package to Combat Antimicrobial Resistance.* 2011. <http://www.who.int/world-health-day/2011/policybriefs/en/index.html> (accessed 23 May 2012).

WEB APPENDIX

W1. **Pelouze PS.** Epididymitis, In: Pelouze PS ed. *Gonorrhoea in the male and female.* Philadelphia: WB Saunders, 1941, p. 240.

W2. **Unemo M,** Shafer WM. Antibiotic resistance in *Neisseria gonorrhoeae*: origin, evolution, and lessons learned for the future. *Ann N Y Acad Sci* 2011;**1230(1)**:E19-28.

W3. **Lewis DA.** The gonococcus fights back: is this time a knock out? *Sex Transm Infect* 2010;**86**:415-21.

W4. **Dan M.** The use of fluoroquinolones in gonorrhoea: the increasing problem of resistance. *Expert Opin Pharmacother* 2004;**5**:829-54.

W5. **Lewis DA,** Marumo E. Revision of the national guideline for first-line comprehensive management and control of sexually transmitted infections: what's new and why? *S Afr J Epid Infect* 2009;**24**:6-9.

W6. **Centers for Disease Control and Prevention.** Update to CDC's sexually transmitted diseases treatment guidelines, 2006: Fluoroquinolones no longer recommended for treatment of gonococcal infections. *MMWR Morb Mortal Wkly Rep* 2007;**56**:332-6.

W7. **Johnson SR,** Sandul AL, Parekh M, *et al.* Mutations causing in vitro resistance to azithromycin in *Neisseria gonorrhoeae*. *Int J Antimicrob Agents* 2003;**21**:414-9.

W8. **Chisholm SA,** Neal TJ, Alawattagama AB, *et al.* Emergence of high-level azithromycin resistance in *Neisseria gonorrhoeae* in England and Wales. *J Antimicrob Chemother* 2009;**64**:353-8.

- W9. **Galarza PG**, Abad R, Canigia LF, *et al.* New mutation in 23S rRNA gene associated with high level of azithromycin resistance in *Neisseria gonorrhoeae*. *Antimicrob Agents Chemother* 2010;**54**:1652-3.
- W10. **Starnino S**, Stefanelli P, *Neisseria gonorrhoeae* Italian Study Group. Azithromycin-resistant *Neisseria gonorrhoeae* strains recently isolated in Italy. *J Antimicrob Chemother* 2009;**63**:1200-4.
- W11. **Katz AR**, Komeya AY, Soge OO, *et al.* *Neisseria gonorrhoeae* with high-level resistance to azithromycin: case report of the first isolate identified in the United States. *Clin Infect Dis* 2012;**54**:841-3.

La seria amenaza de la gonorrea multidrogo-resistente e intratable: la urgente necesidad de una acción global para controlar la propagación de la resistencia a los antimicrobianos, y mitigar el impacto en la salud sexual y reproductiva



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Las ITS siguen siendo una de las principales causas de morbilidad y mortalidad en el mundo entero. La OMS estima que >498 millones de casos nuevos de sífilis, gonorrea, infección por clamidia y tricomoniasis ocurrieron a nivel global en el 2008 en adultos (entre 15-49 años). Más de 106 millones fueron infecciones gonocócicas.¹ En consecuencia, la gonorrea sigue siendo un gran problema de salud pública global con serias consecuencias de salud, sociales y económicas. Un control y tratamiento inadecuado podría traer como resultado severas complicaciones, como la enfermedad pélvica inflamatoria que ocasiona infertilidad o embarazos ectópicos, e infecciones oculares neonatales que pueden ocasionar ceguera. Hasta un 10% de las mujeres que no reciben tratamiento (o reciben tratamiento inadecuado) para infecciones por clamidia o gonorrea podrían volverse infértiles. La gonorrea urogenital es además asintomática en al menos un 50% de las mujeres, lo cual

ocasiona que estas infecciones no sean detectadas ni tratadas, corriendo el riesgo de severas complicaciones. A escala global, hasta 4000 neonatos, anualmente, podrían contraer ceguera debido a infecciones oftálmicas neonatales gonocócicas y por clamidia.² En los hombres, las infecciones gonocócicas causan uretritis sintomática la cual, si no se trata, podría resultar en una epididimitis en 10% a 30% de los casos^{w1}, la que puede llevar a infertilidad. La gonorrea asimismo incrementa de manera significativa la transmisión de VIH. La carga de infecciones gonocócicas es mayor en los países que tienen menos posibilidades de manejarlas debido a diversos factores, incluyendo estigma, recursos inadecuados y falta de pruebas diagnósticas apropiadas, búsqueda de casos y vigilancia y tratamiento antimicrobiano. El problema se hace más complejo debido a la capacidad de la *Neisseria gonorrhoeae* para desarrollar resistencia antimicrobiana (AMR)

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en un periodo relativamente corto.^{3 w2 w3}

Históricamente, desde el advenimiento de la era antibiótica, las infecciones gonocócicas han sido fáciles de tratar. Sin embargo, la susceptibilidad de *N gonorrhoeae* a las sulfonamidas y penicilinas desde mediados de los 1930s y mediados de los 1940s, respectivamente, se ha ido perdiendo gradualmente a medida que el organismo desarrolló un número de mecanismos para la resistencia antimicrobiana. Los años 1980s (mediados) y los inicios de los 1990s se mostraban promisorios con la introducción de tratamientos efectivos de una sola dosis que podían ser administrados oralmente, tal como las fluoroquinolonas (mayormente ciprofloxacina y ofloxacina) y cefalosporinas orales de tercera-generación (siendo cefixima la más potente). El macrólido azitromicina resultó aún más impresionante ya que podía tratar tanto la infección gonocócica como las infecciones por clamidia mediante un régimen de una sola dosis oral. No obstante, la

resistencia a las fluoroquinolonas surgió tan solo después de una década aproximadamente, y estas fueron abandonadas como tratamiento de primera línea empírico para la gonorrea en la región Asia-Pacífico ya en la segunda mitad de los 1990s y a continuación, en EEUU, Europa y partes de África.^{3 w2 w3ew6} La *N gonorrhoeae* resistente a la azitromicina surgió en la segunda mitad de los 1990s,^{4 w7} y a continuación, también se describió un alto nivel de resistencia a la azitromicina en diversos países.^{5 w8ew11}

Así, desde inicios de los 2000s, las cefalosporinas de tercera generación (mayormente cefixima y ceftriaxona) han sido la única clase de antimicrobianos recomendados como tratamiento de primera línea empírico.^{3 w2 w3}

Resulta preocupante que se haya encontrado resistencia y tratamientos fallidos con cefixima en Japón⁶ y más recientemente en Europa.^{7e9} El reciente reporte de una cepa de *N gonorrhoeae* en Japón que era altamente resistente a la ceftriaxona parenteral asociada con una probable falla en el tratamiento con ceftriaxona,¹⁰ la última opción que quedaba para el tratamiento empírico, ha hecho sonar la alarma del gran reto futuro para el tratamiento y control de las infecciones gonocócicas y sus complicaciones. Esto fue seguido además de la identificación de una cepa con alta resistencia a la ceftriaxona en Francia¹¹ y en España.¹² Lo que es más, muchas regiones, alrededor del mundo, describen una decreciente susceptibilidad a la ceftriaxona, y se ha publicado reportes de tratamientos fallidos con ceftriaxona para infecciones faríngeas gonocócicas.^{3 13 w2 w3}

Dada la habilidad de la *N gonorrhoeae* para desarrollar AMR dentro de un tiempo relativamente corto lapso de tiempo complicado con su

habilidad para conservar la resistencia a antibióticos previos, incluso luego de que su uso ha sido discontinuado, **la amenaza de una diseminación de la gonorrea resistente a la ceftriaxona e intratable bajo ciertas circunstancias es real.**^{3 10 11 w2 w3}

La tendencia global de AMR en *N gonorrhoeae*, su susceptibilidad disminuida y su resistencia a las cefalosporinas de tercera-generación, en una era de viajes internacionales frecuentes ha dictado que se necesite elaborar una estrategia global para responder a la emergente amenaza de una gonorrea intratable. Esto es especialmente importante debido a que los datos sobre AMR gonocócico no estuvieron disponibles en diversos lugares, y la verdadera magnitud global del problema se desconoce. Por ello, el Programa de Vigilancia Antimicrobiana Gonocócica Global de la OMS (WHO Global GASP), inicialmente establecido en los 1990s, fue revisado y rediseñado el 2009 como una red de colaboradores con el fin de permitir una respuesta global coordinada. La red GASP está ubicada en las oficinas centrales de la OMS, Ginebra, como centro focal de gestión trabajando con colaboradores interregionales en África, Asia, las Américas, Europa y el Pacífico Occidental, y procura alentar y reclutar laboratorios nacionales para monitorear los datos de la AMR gonocócica, dando particular atención a las cefalosporinas de tercera-generación, e identificando fallas de tratamiento cuando se utiliza el tratamiento recomendado.

Para facilitar el funcionamiento de la red GASP e involucrar el apoyo de los gobiernos y donantes de la comunidad internacional en esta aventura, la OMS publicó el 'Plan de Acción Global para Controlar la Diseminación y el Impacto de la Resistencia Antimicrobiana de *N gonorrhoeae*' en Junio del

2012.¹⁴ El Plan de Acción Global busca facilitar la detección temprana de cepas resistentes al tratamiento recomendado, en combinación con una respuesta de salud pública para mitigar el impacto de la *N gonorrhoeae* resistente a la cefalosporina en la morbilidad de salud sexual y reproductiva. El Plan de Acción Global de la OMS llama a una respuesta desde la salud pública para el control de las infecciones gonocócicas y el surgimiento de la gonorrea multidrogo-resistente e intratable. Algunos de los principales componentes y acciones del Plan de Acción Global son:

< Abogar por una mayor conciencia en el uso correcto de los antibióticos entre los proveedores de servicios de salud y los consumidores, en particular dentro de las poblaciones clave, incluyendo a los hombres que tienen sexo con otros hombres y las trabajadoras sexuales.

< Una efectiva prevención, diagnóstico y control de la gonorrea, usando mensajes de prevención, intervenciones, regímenes recomendados de diagnóstico y tratamiento.

< El monitoreo sistemático y la detección temprana de fallas de tratamiento usando el tratamiento recomendado (cefixima y ceftriaxona) mediante el desarrollo de una definición estándar de falla de tratamiento, y protocolos para la verificación, reporte y manejo de las fallas.

< Políticas efectivas para la regulación y prescripción de fármacos.

< Supervisión intensiva de la AMR, especialmente en países con una alta carga de infecciones gonocócicas (y/o AMR gonocócica), otras ITS y VIH.

< Construir la capacidad para establecer redes regionales de laboratorios que realicen cultivos gonocócicos de calidad asegurada y pruebas de susceptibilidad antimicrobiana.

< Investigar para identificar nuevos

métodos moleculares para detectar y monitorear la resistencia antimicrobiana.

< Investigar (ciencia básica, in vitro y estudios clínicos) para identificar estrategias alternativas de tratamiento y/o antimicrobianos efectivos (u otros compuesto efectivos) para la gonorrea.

Este Plan de Acción Global será implementado dentro de la Estrategia Global de la OMS para la Prevención y Control de Infecciones de Transmisión Sexual 2006-2015' que fue adoptado por los países miembros de la OMS en la 59ava Asamblea Mundial de la Salud en Mayo del 2006.² Para asegurar la armonización y sostenibilidad, la red GASP será enlazada con, y operará dentro del Paquete de Políticas de la OMS para Combatir AMR que fuera lanzada en el Día Mundial de la Salud 2011 en Ginebra.¹⁵

La implementación de las actividades de la GASP tanto a nivel global como nacional solo se podrá lograr mediante la formación de alianzas para financiamiento y entrenamiento entre programas distintos pero relacionados, y un adecuado financiamiento para la vigilancia de las ITS, en general, y pruebas de AMR gonocócicas de calidad asegurada, en particular. Diversos planes de acción específicos por región e incluso específicos por país para controlar la diseminación de la resistencia antimicrobiana gonocócica, también están en etapa de preparación, estos planes son también cruciales para la respuesta global ante la seria amenaza de la gonorrea intratable. Por último, es esencial identificar nuevas estrategias y/o antimicrobianos (u otros compuestos efectivos) para el tratamiento efectivo de la gonorrea. Es imperativo que esta investigación sea adecuadamente apoyada y financiada por los socios nacionales e internacionales.

REFERENCIAS

1. World Health Organization. Global Prevalence and Incidence Of Selected Curable Sexually Transmitted Infections 2008: Overview and Estimates. Geneva, 2012. http://www.who.int/reproductivehealth/publications/rtis/2008_STI_estimates.pdf (accessed 6 Jul 2012).
2. World Health Organization. Global Strategy For The Prevention And Control of Sexually Transmitted Infections: 2006-2015. Geneva, 2007. ISBN: 978 92 4 156347 5. <http://www.who.int/reproductivehealth/publications/rtis/9789241563475> (accessed 28 May 2012).
3. Tapsall JW, Ndowa F, Lewis DA, et al. Meeting the public health challenge of multidrug- and extensively drug-resistant *Neisseria gonorrhoeae*. *Expert Rev Anti Infect Ther* 2009;7:821-34.
4. Dillon JA, Ruben M, Li H, et al. Challenges in the control of gonorrhoea in South America and the Caribbean: monitoring the development of resistance to antibiotics. *Sex Transm Dis* 2006;33:87-95.
5. Palmer HM, Young H, Winter A, et al. Emergence and spread of azithromycin-resistant *Neisseria gonorrhoeae* in Scotland. *J Antimicrob Chemother* 2008;62:490e4.
6. Yokoi S, Deguchi T, Ozawa T, et al. Threat to cefixime treatment of gonorrhoea. *Emerg Infect Diseases* 2007;13:1275e7.
7. Ison CA, Hussey J, Sankar KN, et al. Gonorrhoea treatment failures to cefixime and azithromycin in England, 2010. *Euro Surveill* 2011;16:19833.
8. Unemo M, Golparian D, Syversen G, et al. Two cases of verified clinical failures using internationally recommended first-line cefixime for gonorrhoea treatment, Norway, 2010. *Euro Surveill* 2010;15:19721.
9. Unemo M, Golparian D, Stary A, et al. First *Neisseria gonorrhoeae* strain with resistance to cefixime causing gonorrhoea treatment failure in Austria, 2011. *Euro Surveill* 2011;16:19998.
10. Ohnishi M, Golparian D, Shimuta K, et al. Is *Neisseria gonorrhoeae* initiating a future era of untreatable gonorrhoea? Detailed characterization of the first strain with high-level resistance to ceftriaxone. *Antimicrob Agents Chemother* 2011;55:3538-45.
11. Unemo M, Golparian D, Nicholas R, et al. High-level cefixime- and ceftriaxone-resistant

N. gonorrhoeae in France: novel penA mosaic allele in a successful international clone causes treatment failure. *Antimicrob Agents Chemother* 2012;56:1273-80.

12. Ca'mara J, Serra J, Ayats J, et al. Molecular characterization of two high-level ceftriaxone-resistant *Neisseria gonorrhoeae* isolates detected in Catalonia, Spain. *J Antimicrob Chemother*. Published Online First: 7 May 2012. doi:10.1093/jac/dks162

13. Unemo M, Golparian D, Hestner A. Ceftriaxone treatment failure of pharyngeal gonorrhoea verified by international recommendations, Sweden, July 2010. *Euro Surveill* 2011;16:19792.

14. World Health Organization. Global action plan to control the spread and impact of antimicrobial resistance in *Neisseria gonorrhoeae*. 2012. ISBN: 978 92 4 150350 1. <http://www.who.int/reproductivehealth/publications/rtis/9789241503501> (accessed 28 May 2012).

15. World Health Day. Policy Briefs/WHO Policy Package to Combat Antimicrobial Resistance. 2011. <http://www.who.int/world-health-day/2011/policybriefs/en/index.html> (accessed 23 May 2012).