ReAct facts

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Burden of Antibiotic Resistance on Women's Health

◆ Sepsis is still one of the major causes of death following abortion and childbirth. Resistance is common among several of the bacterial species causing infections, but in spite of the serious consequences, the size as well as the burden of such resistance is to a large extent unknown.

◆ Infections during pregnancy may also lead to pre-term delivery, stillbirth and death of the infant in sepsis. As long as the prevalence of antibiotic resistance is almost unknown, and the urgent need of new effective antibiotics is not being provided for, adequate treatment of the mother and her child cannot be guaranteed.

◆ Improvement of maternal health as stated in Millennium Development Goal (MDG) 5 will be difficult to achieve for such reasons.

◆ Antibiotic resistance may also be a serious problem when women contract sexually transmitted infections (STI), especially gonorrhoea. Untreated or untreatable infections may lead to pelvic inflammatory disease, causing chronic pain and discomfort, infertility, and ectopic pregnancies. Newborn babies may become blind.

◆ An estimated 3 million treatment failures due to resistant gonorrhoea occur each year in the world and will incur an additional cost of US$ 500 million. When treatment guidelines recently had to be changed in the US, due to increasing resistance to ciprofloxacin, the cost of treatment increased fivefold. The risk of HIV-transmission increases considerably if STI are impossible to treat adequately.

SCOPE OF THE PROBLEM

Infections in the female genital tract – RTI (reproductive tract infections) – include endogenous infections as well as iatrogenic and sexually transmitted infections (STI).[1] Infections during pregnancy and after childbirth may follow any of these. Resistance to antibiotics commonly used for treating such infections has emerged in many parts of the world.[2] However, data is lacking or very scarce regarding the burden of antibiotic resistance within the field of women´s health, although the consequences can be severe.

Infections following abortions, pregnancy and childbirth

With the institution of antiseptic practices and later the availability of antibiotics, the incidence of puerperal sepsis decreased considerably, but it is still, along with haemorrhage, one of the

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main causes of maternal deaths worldwide.[3,4,5]

Infections include metritis, pelvic cellulitis and abscess, peritonitis following uterine perforation, and septicemia.[6]

STI and other infections of the genital tract

Untreated infections increase the probability of acquisition and transmission of HIV. [7,8]

An estimated 340 million cases of curable STI occur annually in adults. Most are in south and south-east Asia and sub-Saharan Africa. Infections may lead to acute and chronic symptoms and long term consequences.

As many as 70% of infections in women may be asymptomatic.[9] Infections during pregnancy can have adverse effects and may cause infections in the newborn baby.

Syphilis during pregnancy may result in stillbirth, neonatal death or congenital syphilis.

STI caused by *Clamydia trachomatis* and *N. gonorrhoeae*:

If not treated adequately, complications may lead to pelvic inflammatory disease (PID), infertility, chronic pain and ectopic pregnancies.[9] 40-50% of ectopic pregnancies can be attributed to earlier PID. Transmission of infection to the infant during birth may lead to blindness and in the case of *C. trachomatis* also to pneumonia.

EPIDEMIOLOGY

Sepsis following abortion

An estimated 19-20 million unsafe terminations take place each year in the world, and around 68,000 women die as a consequence, which accounts for about 13% of all pregnancy related deaths in the world.[10,11,12] Deaths due to abortion are most common in the Caribbean and Latin America. The specific cause of death is often unknown but is considered to be haemorrhage or sepsis in most cases. In a study in Malawi, 77.1% of the deaths after abortions were due to sepsis.[4]

There is so far no knowledge about the impact of antibiotic resistance when fatal infections occur.

Puerperal sepsis and infections during pregnancy

More than 500,000 women die each year due to complications during pregnancy and childbirth.[3, 13] Sepsis is estimated to be the cause of maternal deaths in 0.5-15% of cases. It is significantly more common in Africa, Asia, Latin America and the Caribbean than in developed countries.[3] Infection occurs even more often after Caesarean section.[14,15] On rare occasions amniocentesis may also lead to serious infections.[16]

STI

An estimated 62 million cases of gonorrhoea occur each year in the world.[9]

In the US, reported rates of gonorrhoea and *C. trachomatis* infections among women were respectively 124.3 and 515.8 per 100,000 in 2006.[17] Infection may be 10-100 times more common in low-income communities according to the WHO.

Syphilis

More than 1 million infants are born with congenital syphilis each year in the world.[18]

In the US, syphilis in women is much more uncommon than in men and increased by 11.1% in 2006 to one case per 100,000. Three hundred and forty nine cases of congenital syphilis were reported there in 2006.[17]

COMMON PATHOGENS

Infections are often caused by several species of bacteria. *E coli,* beta haemolytic streptococci, *S aureus* and anaerobes are all common pathogens.[6, 15, 19, 20] Other agents include Klebsiella spp, enterococci, and *N. gonorrhoeae*. *C. trachomatis* and Mycoplasma species may also be responsible, as may (rarely) Clostridia.[6]

Antibiotic resistance

Effective and early treatment of STI is essential to decrease the transmission of the actual disease, and of HIV. The choice of antibiotic for treatment depends on knowledge of local resistance patterns. As an example, since 2007 ciprofloxacin is no longer recommended by the CDC as the first-line treatment for gonorrhoea in the US due to high level of resistance.[28, 32] The same decision had to be made in India.[34] Penicillins have remained effective for the treatment of early syphilis.[31]

Resistance among aerobic Gram-negative bacteria like *E. coli* is common and several strains are also resistant to third-generation cephalosporins (see factsheet on MRGN). *E. coli* carried as part of the normal flora can be resistant, and maternal colonisation with resistant bacteria may lead to neonatal sepsis.[21] Prophylactic treatment given against Group B streptococci may lead to neonatal infections with resistant bacteria, e.g. *E coli*.[22-24]

The number of community- and hospital-associated methicillin resistant *S. aureus* (MRSA) infections is increasing in the post-partum period.[20,25,26]

Two out of 305 women screened had vaginal colonisation with MRSA.

Penicillinase-producing *N. gonorrhoeae* (PPNG) emerged in 1976. Surveillance programmes in several countries,[27, 28, 29] and the global gonococcal antimicrobial surveillance programme (GASP) of the WHO monitor development of resistance among *N. gonorrhoeae*. In the US, 19.6% of *N. gonorrhoeae* were resistant to penicillin, tetracycline or both in 2005, an increase from 15.9% in 2004.[5] In the

ReAct
Action on Antibiotic Resistance

- ReAct links a wide range of individuals, organisations and networks around the world taking concerted action to respond to antibiotic resistance.
- Our vision is that current and future generations of people around the globe should have access to effective treatment of bacterial infections.
- ReAct believes that antibiotics should be used appropriately, their use reduced when of no benefit and their correct and specific use increased when needed.
- ReAct believes that awareness of ecological balance is needed as part of an integral concept of health.

UK, 17.9% of isolates were penicillin-resistant in 2005 but the figure fell to 9.5% in 2006. Tetracycline resistance was present in 36.9% of isolates, again a decrease from 48%.[27] In India, penicillin resistance increased significantly to 68.4% in 2003 but decreased to 18.2% in 2006. In other parts of Asia, 9-90% of isolates are penicillin-resistant, as are over 35% in sub-Saharan Africa.[2]

Resistance to fluoroquinolones is increasingly prevalent globally. The prevalence in Hongkong and other parts of China is 99%.1 In India resistance to ciprofloxacine increased to 97.2% in 2006.[34]

Overall quinolone resistance among *N. gonorrhoeae* has increased steadily to around 13% in the US in 2006[28] and to 21.7% in the UK in 2005.[27]

Confirmed resistance to ceftriaxone has still not been recorded worldwide but isolates with intermediate susceptibility have been identified.[28]

In India, 5,5% of isolates were less susceptible in 2006.[34] Resistance to cefixime has not yet been identified.

Isolates with higher azithromycin MIC were also found to have increased over the years, and 5% of the isolates were resistant to azithromycin in Europe in 2004.[29] In the Caribbean and South America, these figures vary from 16% to 70%.[2]

Resistance to spectinomycin varies from 0% to about 5%.[2]

Antibiotic resistance among *C. trachomatis* is still low, but in vitro resistance to macrolide antibiotics has been detected.[30] Since 2002 treatment failures have occurred in the US when early syphilis has been treated with azithromycin. A high prevalence of the resistant bacteria has also been found in Ireland.[31]

QUALITATIVE CONSEQUENCES OF RESISTANCE

Infections due to resistant bacteria can be severe and may require readmission, intensive and prolonged care, and facilities for culture and susceptibility testing. Mortality increases if initial therapy is inappropriate. Excess cost of therapy is high.

> The risk of HIV-transmission increases considerably if STI are imposible to treat adequately

Individual

- ☐ Increased mortality and morbidity, e.g. chronic pelvic inflammatory disease (PID) with infertility, chronic pain, ectopic pregnancy with severe consequences[33]
- ☐ High cost of second-line treatment and hospital care
- ☐ Psychological effects
- ☐ Loss of child

Hospital

- ☐ Increased cost of diagnostic procedures and care
- ☐ High costs of alternative drugs, which may have to be administered i.m.
- ☐ Availability of drugs
- ☐ Need for higher level of care, possibility of emergency operations (in the case of ectopic pregnancies), increased workload for healthcare personnel

Societal

- ☐ Maternal death with far-reaching consequences for the whole family, long-term illness and lack of productivity
- ☐ Stillbirths or deaths of newborn babies; need for care of sick newborn babies
- ☐ Need for care of orphans
- ☐ Need for care of disabled children
- ☐ Increased transmission of HIV

QUANTITATIVE CONSEQUENCES OF RESISTANCE

Quantification of morbidity, mortality or costs due to antimicrobial resistance associated with infections during pregnancy or delivery is impossible for the time being because of lack of reliable data. Difficulties include inadequate diagnostics, uncertain aetiology of infections, other coexisting conditions (haemorrhage, ecclampsia etc) and sometimes lack of proper records.

Based on figures from the USA, an assumption of 3 million treatment failures globally each year due to antibiotic resistance in gonorrhoea has been made. This would incur an extra cost of US$ 500 millions each year.[35] The cost of treatment of resistant go norrhoea is five times higher when ciprofloxacin has had to be replaced by ceftriaxone. The cost of treatment of MRSA infections is probably three times higher than that incurred by susceptible strains.

Dearth of resources

- ☐ Lack of access to skilled antenatal care
- ☐ Lack of safe conditions during childbirth
- ☐ Lack of access to effective contraceptives and safe abortions
- ☐ Lack of adherence to STI management programmes
- ☐ Lack of quality-assured culture and antimicrobial susceptibility testing facilities
- ☐ Lack of adequate and affordable drugs for treatment
- ☐ Lack of knowledge about overuse or misuse of medicines

Urgent needs

- ☐ Train caregivers in appropriate infection control and rational drug use.
- ☐ Improve diagnostic capacity and documentation of infection, aetiological agents and their antimicrobial susceptibilities.
- ☐ Develop hospital-based and community-based surveillance systems to monitor antibiotic resistance trends, antibiotic use and treatment failure rates.
- ☐ Perform clinical trials to identify the most effective drugs/combinations for specific indications.
- ☐ Develop locally relevant guidelines, taking into account local susceptibility patterns, availability and cost of drugs, diagnostic facilities etc.
- ☐ Develop new medicines which can cure STI and other infections suffered by women.

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