broader involvement of the RET signalling-network in the pathogenesis of the disease. The observations in the same Hirschsprung's disease patients of mutations in *RET* with mutations in related proteins are consistent with the concept of synergistic heterozygosity.[8,9] In this concept, partial compromise of two or more steps in a pathway may be equivalent in terms of phenotypic consequence to more complete compromise of a single step. A corollary to this concept is that if mutations in two or more related genes are observed in a patient, the protein products of these genes may be presumed to be involved in the same pathogenetic pathway or network. Going further, mutations in other proteins among patients with this phenotype (eg, Hirschsprung's disease) indicate that these additional proteins are related biologically, either directly or indirectly, to the other proteins in which mutations are associated with this phenotype.

A proteomic network involved in the pathogenesis of Hirschsprung's disease can be drawn, based on the work reviewed by Fitze and colleagues and including recognised and putative protein-protein interactions (panel). The interacting proteins (solid lines) form subnetworks. Subnetworks without recognised biological relations interact through their involvement in the pathogenesis of the Hirschsprung's disease phenotype (dashed arrows). The dashed arrows and phenotypic designation remain as a "black box" in this network until direct proteomic relations with other network components are elucidated. This network has the hub-and-spoke architecture of highly robust, scale-free networks.[4] Network dynamics must be understood to relate alterations in primary genes and modifiers to patients' phenotypes.[2–4] The complexity of these interactions is further shown by the inter-relations between Hirschsprung's disease and the type 2 multiple endocrine neoplasias (MEN2). Whereas, in general, Hirschsprung's disease is thought to be due to *RET* loss-of-function mutations and MEN2 to gain-of-function mutations, MEN2A or MEN2B has been observed in association with Hirschsprung's disease.[10,11]

The extended genotype for each individual patient will be rare. The affected individual's genotype will represent selected mutations in one or more primary genes, and modifying sequence-variations in the genes in the proteomic network and other genes influencing expression of network components. Although the number of genes involved in the extended network is large, for the individual patient a smaller subset of genes will be involved. This concept will also be true for patients with common disease phenotypes, such as diabetes mellitus, heart disease, or cancer: while the genes involved are presumed to be even more numerous, not all of these genes will be affected in any one individual. The smaller subset involved in the individual patient will represent a relatively unique genotype, because the number of possible combinations will be large.

For all of these reasons Hirschsprung's disease gives informative insights into the pathogenesis of rare as well as common disease phenotypes. Investigations of complexity in biological networks at the fundamental level and translation of this information into clinical medicine will eventually allow prediction of an individual's phenotype from their extended genotype.

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Severe pneumonia and a second antibiotic

Since there are no unique clinical features that accurately identify the specific respiratory pathogen when a patient is first seen in hospital with community acquired pneumonia (CAP), empirical antibiotic therapy is started pending the results of microbiological investigations. Most published guidelines advocate choosing the initial empirical antibiotic therapy based on assessment of the severity of the pneumonia and a knowledgeable guess at the likely pathogen(s), with adequate cover for pneumococcal pneumonia being the essential pre-requisite. *Streptococcus pneumoniae* is the commonest cause of CAP and the pathogen causing most deaths. All three CAP management guidelines published recently from North America[1-3] recommend combination antibiotic therapy initially for patients with severe pneumonia, typically an intravenous β-lactamase-stable, β-lactam with an intravenous macrolide or intravenous "anti-pneumococcal" fluoroquinolone. The recent British Thoracic Society guidelines[4] make similar recommendations and also advise combined empirical oral therapy for adults in hospital with non-severe CAP to cover both bacterial and atypical pathogens. Guidelines vary somewhat about the features used to identify a patient with severe CAP at the time of admission to hospital (panel).

About one in five patients with untreated pneumococcal pneumonia will have associated bacteraemia, a feature linked with severe illness and a worse prognosis.[5] It is therefore interesting to note a recently published retrospective review by Grant Waterer and colleagues,[6] which concludes that adults with severe bacteraemic pneumococcal pneumonia have a significantly greater risk of death (odds ratio 6·4, 95% CI 1·9–21·7) if they receive a single antibiotic rather than combination antibiotics on the first day of admission. The investigators describe all their patients as having "severe" pneumonia and used the pneumonia severity index[7] to predict mortality (these scores were not designed to triage individual patients).

Two definitions of severe pneumonia, by which patients should receive initial combined antibiotic therapy*

American Thoracic Society guidelines[3]	**British Thoracic Society guidelines**[4]
Presence of two or more minor criteria	Presence of two or more "core" adverse prognostic features (CURB score):
Low blood pressure (systolic ⩽90 or diastolic ⩽60 mm Hg)	**C**onfusion
Severe respiratory failure (PaO_2 /FiO_2 ratio of <250)	**U**rea raised (>7 mmol/L)
Bilateral or multilobe radiographic shadowing	**R**espiratory rate raised (⩾30/min)
	Blood pressure low (systolic <90 or diastolic ⩽60 mm Hg)
Additional adverse prognostic features that may help initial clinical judgment in assessing severity	
Confusion, respiratory rate raised (⩾30/min), urea raised (>19·6 mg/dL)	Age 50 years or over, coexisting chronic disease, hypoxia (PaO_2 <8 kPa /SaO_2 <92%: any FiO_2), bilateral or multilobe radiographic shadowing

*Based on information available at time of hospital admission. Urea: 1 mg/dL=0·035 mmol/L.

How could this finding be explained? The researchers consider several theoretical possibilities, none of which sound convincing, such as a synergistic effect of antibiotic agents, in-vivo differences in the killing rate of pneumococci after different antibiotic exposure, and alteration of the immune response by antibiotics. (In this study, patients with penicillin-resistant pneumococcal isolates were excluded.) The presence of mixed infections could be the most likely explanation. Among 358 cases of pneumococcal pneumonia,[8-10] there was a high frequency (>50%) of other infections as detected by various microbiological tests: other bacteria in 11% (mostly *Haemophilus influenzae*); atypical pathogens, such as *Chlamydia pneumoniae* or *Chlamydia* spp and *Mycoplasma pneumoniae* in 21% and 16%, respectively; legionella infection in 6%; and viruses in 20%. It is likely that most clinicians would feel compelled to cover any identified co-pathogens in a patient with severe CAP, but it is uncertain whether the presence of co-pathogens, such as *C pneumoniae*, generally identified by serological methods, or treatment of such organisms substantially affects outcome.

How likely is it that the conclusion of this study, that combination therapy is beneficial for severe pneumococcal bacteraemic pneumonia, is correct, based on the data presented and potential confounding factors? The researchers are open in discussing the potential weaknesses of the study. The route or dose of antibiotic is not reported, nor is whether patients were offered comparable supportive care, such as admission to intensive-care units, or had a similar history of pneumococcal vaccination. Mortality rates of pneumococcal bacteraemia vary greatly between centres,[11] suggesting that factors in addition to antibiotic therapy are important. Also, was the antibiotic changed after the result of the blood culture was known? The investigators only analysed the results by the antibiotics given in the first 24 h after presentation, arguing that subsequent antibiotic changes would not be likely to influence outcome. Although some patients died shortly after admission, half of the deaths occurred after 5 days and mortality rates continued to increase throughout the 15-day study, suggesting that subsequent antibiotic therapy might be an important determinant of outcome. Over half of the cases received fluoroquinolone monotherapy (mostly levofloxacin), which raises the concern that this drug alone may not be sufficient for severe bacteraemic pneumococcal pneumonia in the dose given. None of the recent guidelines recommend fluoroquinolones as sole treatment for patients with severe CAP,[1-4] and failure of treatment of pneumococcal pneumonia with oral levofloxacin has been reported and associated with resistance to fluoroquinolones.[12] In fact as many deaths in the monotherapy group occurred with third-generation cephalosporins, a finding similar to that from a multicentre study of 460 adults with pneumococcal bacteraemia in which mortality was lowest for penicillin therapy and highest for cephalosporin therapy,[11] findings that are difficult to explain.

What should be done in the future? The investigators recommend a double-blind trial of single versus combination therapy for patients with severe CAP (pneumonia severity index IV and V in which risk of death is greater than 8% and 27%, respectively) and suspected bacteraemic pneumococcal pneumonia, but it is difficult to see how this is practical unless rapid tests for pneumococcal bacteraemia become available. Urinary pneumococcal antigen can now be detected at the bedside with commercial kits, but the correlation with bacteraemia is weak. In one recent study of 129 patients with pneumococcal CAP, 69 had a positive pneumococcal urine-antigen-test and only nine had positive blood cultures.[9]

What Waterer and colleagues' study does emphasise is the importance and potential seriousness of pneumococcal pneumonia. The need to cover this pathogen effectively in any empirical antibiotic regimen for CAP remains a priority.

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Violence against women: a global burden

See page 1232

At least one in five women have been physically or sexually abused by a man at some time in their lives.[1] According to the World Bank, gender-based violence accounts for as much death and ill-health in women aged 15–44 years as cancer, and is a greater cause of ill-health than malaria and traffic accidents combined.[2] G8 leaders have set ambitious targets for reducing the global burdens of disease caused by tuberculosis, malaria, and HIV/AIDS by 2010, but why does violence against women, a massive cause of morbidity and mortality, remain overlooked by governments? Not for any lack of awareness; many conferences, policy statements, and reports have highlighted and debated the problem. For example, in 1996, the United Nations Development Fund for Women (UNIFEM) established a trust fund to provide direct support to hundreds of women's development and empowerment projects around the world. In 1999, the UN designated Nov 25 the International Day for the Elimination of Violence Against Women. In October, 2001, Johns Hopkins University Center for Communication Programs launched an information and resource website entitled End Violence Against Women. In 1993, one of the most comprehensive international policy statements on gender-based violence, the Declaration against Violence against Women, was adopted by the UN General Assembly. And, later this year, WHO will launch the first Global Report on Violence and Health, with one of seven topic-specific chapters devoted to violence by an intimate partner.

Starting today in *The Lancet*, for 6 weeks, Charlotte Watts and Rachel Jewkes present a series that provides a comprehensive overview of the health issues central to violence against women: global prevalence and definitions of violence against women, health consequences, prevention, health-sector response, research ethics, and perhaps most disturbingly, violence perpetrated within health-care organisations. One of the key issues to emerge is that inequalities in gender and income are the principal causes of violence. One of the more shocking findings is the fact that health-care workers are often themselves the problem, rather than the solution.

So what can be done? Laws alone are not enough—violence against women in Bangladesh is rising steeply despite tough laws introduced to tackle the problem.[3] Prevention should be seen in terms of economic and educational empowerment of women in broad terms. "Eradicating violence against women requires coordinated action and commitment by many actors; including governments, civil society, the judiciary, police, media, health-care workers, educators and the international community", argues Noeleen Heyzer, Executive Director of UNIFEM. Successful interventions are those that address the status of women: economically, in societal attitudes, in interpersonal relationships, and in communities. Few studies have assessed the effect of economic interventions on gender violence. Such interventions have generally consisted of small-scale microcredit schemes[4] whose effectiveness can vary between settings: although considerable economic empowerment is protective, a little empowerment can actually increase the risk of violence as men seek to maintain control of the household finances.

Context is also important. A recent study of American women revealed some of the links between sexual assault and wider health issues.[5] For instance, many women who were victims of sexual assault perceived their general health—mental and physical—to be poor. After appropriate social factors had been taken into account, victims of sexual assault smoked more, had higher proportions of hypertension and hypercholesterolaemia, and tended to be overweight. Smoking and obesity may be adaptive responses to violence. But this work also opens up the possibility of screening for sexual violence in women attending general medical clinics.

It is tempting to suggest that the shift in attitude required at all levels of society is too enormous to be contemplated by a world in which patriarchy still dominates personal and political life. With the increasing feminisation of poverty,[6] economic inequalities urgently need to be addressed. Central to this process is the need to support women's unpaid work as carers, in the home and in communities. Public resources need to be invested to enable access to affordable food, water, and shelter, and to set up childcare facilities. These interventions "not only enable women to access paid work, but can have a multiplier effect in terms of enabling children, particularly girls, to go to school".[6] This issue is not relevant only in the developing world; in developed countries women are penalised in terms of wages, pensions, and benefits by the decision to have children.

Violence against women is the extreme end of a sliding scale of discrimination and prejudice against women, and must be addressed as a priority by governments if we are to achieve a just world. But first, doctors and other health-care professionals need to face up to the problem and debate a strategy to deal with it—which is the aim of this series.

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