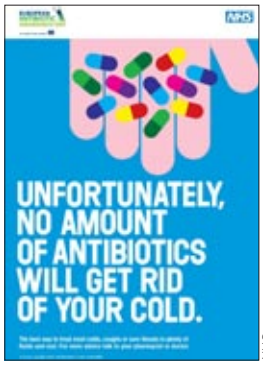
Tackling antibiotic resistance

Concerted action is needed to provide new technologies and conserve existing drugs



NHS

ANALYSIS, p 1115
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The twin challenge of conserving the effectiveness of existing antibacterial drugs and developing new ones is attracting attention in policy circles. In September 2009, a conference organised under the auspices of the Swedish European Union presidency highlighted the need to provide incentives for developing new antibacterial drugs. In the linked article, Morel and Mossialos provide an inventory of incentives, prepared for that conference, to promote research and development for new treatment options.[1]

Last November, the summit between the EU and the United States announced a transatlantic task force on antimicrobial resistance that will tackle "appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities, prevention of both healthcare- and community-associated drug-resistant infections, and strategies for improving the pipeline of new antimicrobial drugs."[2]

In the US, the annual cost of treating resistant nosocomial infections traceable to six bacteria exceeded $1.87bn (£1.2bn; €1.4bn), greater than the yearly cost of treating influenza.[3] In the EU, added costs and loss of productivity as a result of antibiotic resistance conservatively amount to €1.5bn.[4] This problem is not just transatlantic, but global. Tuberculosis claims 1.8 million lives each year, and typhoid fever takes another 200 000.[5] Multidrug resistance has forced clinicians to fall back on second line and third line regimens, which multiplies treatment costs. Especially in developing countries, such cost barriers compound irrational use.

With the announcement of the EU-US task force, the Infectious Diseases Society of America has called for committing to a goal of developing 10 new antibacterial drugs by 2020.[6] Catchy as 10×20 sounds, the public sector strategy for funding such research and development must prioritise among different health technologies, such as diagnostics and vaccines, to combat antibiotic resistance. For example, three million children die each year from acute respiratory bacterial infections in developing countries, but penicillin sensitive pneumococcal strains have declined to a half, even a quarter, in some countries. A diagnostic test for bacterial pneumonia would save an estimated 405 000 lives a year, by targeting treatment and avoiding overprescription of antibiotics.[7] New vaccines may also reduce reliance on drugs as the use of pneumococcal vaccine has suggested.

The incentives for new antibacterials must not only fuel the sprint to goals like 10×20, but must also sustain the marathon of antibiotic development well into the future. With far more lucrative therapeutic categories in which to invest, large firms may ignore research and development in the field of antibiotics. Making the next new antibiotic a blockbuster though is not the solution. Small firms, which face different opportunity costs, may wish to pursue new antibiotics but not have the capital to do so. Rather than rely on extended patent terms or data exclusivity[8]—incentives with payoffs too far down the pipeline—the public sector might focus on enabling greater access to low cost capital and to upstream research tools, such as compound libraries of potential new drugs.

To ensure rational use, these products will also have to be affordable in resource-limited settings. Delinking research and development costs from drug pricing and the return that drug companies receive on investment could correct misaligned economic incentives. But this will require innovative financing approaches, from public financing of clinical trials to prizes.[9 10] If the public sector wants these drugs to be for the public good, then it must carefully invest in the right package of incentives to achieve both innovation and access.

Better financing is only part of the picture. Beyond incentives, the way that innovations are brought from bench to bedside will need to be re-engineered to meet major scientific challenges. Lessons can be learnt from tuberculosis—for which no new drug has been developed in decades and we still rely on century old diagnostic methods. The Global Alliance for Tuberculosis has sought to produce promising drug candidates, even posting prizes on InnoCentive, and its "critical path to tuberculosis regimens" may shave years off the time needed for regulatory approval of combination treatments. India's Council of Scientific and Industrial Research has embarked on an Open Source Drug Discovery initiative. Eli Lilly has transferred the production of cycloserine for treating multidrug resistant tuberculosis to generic drug makers to ensure its continued availability. Although some of these initiatives are fledglings, they represent efforts to rethink traditional paradigms of bringing drugs to market.

Today's dearth in the antibacterial research and development pipeline will take decades to reverse. To complement the strategy to bring new drugs to market, concerted action must be taken now to conserve existing drugs. Strategies to realign economic incentives, fill information gaps, and minimise interruptions in the supply chain will require no less innovation.[11] Proof that antibiotic prescribing contributes to resistance in the individual patient and

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not just at the societal level is the kind of evidence that needs to be communicated to clinicians.[12] Taking a page from the Five Million Lives campaign and the work of the World Alliance for Patient Safety, much more can be done to bolster diagnostics and surveillance of resistance patterns, reduce demand from patients for unnecessary antibiotics, and help standardise optimal dosing regimens and treatment times.

The EU-US Transatlantic Task Force must rise to this complex challenge and define its solution in global terms. Nothing less than the future of medicine, from organ transplants to chemotherapy, is at stake, and there will be no second chances.

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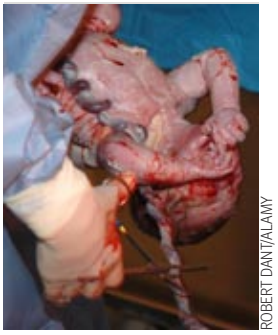
Umbilical cord blood gas analysis

Paired samples should be analysed in selected circumstances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RESEARCH, p 1121

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The umbilical cord, discarded without thought from labour wards for so long, has recently generated interest on several fronts. Cord blood is a source of stem cells and some parents want cord blood collected for banking by commercial enterprises in case it can help their child's future health needs. However, the Human Tissue Authority in the United Kingdom has recently expressed concerns about the safety of collection mechanisms.[1] It is also increasingly recognised that obstetricians and midwives often clamp the cord too soon after birth, thereby depriving the baby of substantial amounts of blood—this is particularly important in parts of the world where infant anaemia is prevalent.[2] And now we have biochemical analysis of cord blood. In the linked systematic review, Malin and colleagues assess the association between umbilical cord pH at birth and outcomes.[3]

Umbilical cord blood gases could be of value in auditing the outcomes of labour, predicting future development of the newborn, helping clinical research, and resolving expensive medicolegal disputes. If the fetus is deprived of adequate oxygenation during labour—for example, through placental malfunction, cord compression, or excessive uterine contractions—the pH drops and the base deficit rises as anaerobic metabolism is activated and lactic acid is produced. Babies with limited metabolic reserve, notably the preterm fetus and those with restricted growth, are less able to withstand the effects of hypoxaemia. However, the clinical guideline from the National Institute for Health and Clinical Excellence in 2007 on intrapartum care was lukewarm about the prognostic importance of low umbilical artery pH values—"cord arterial gas was not regarded as a good predictor of either neonatal death or developing cerebral palsy, even compared with Apgar scores."[4]

In contrast, Malin and colleagues' systematic review of observational data suggests that a strong association exists between low umbilical artery pH at birth and major adverse outcomes including death, hypoxic ischaemic encephalopathy (usually manifesting as neonatal seizures), potentially serious brain abnormalities identified by imaging (periventricular leucomalacia or intraventricular haemorrhage), and cerebral palsy.[3]

Malin and colleagues have been at the forefront of systematic reviews of screening and diagnostic tests in the perinatal field. In their systematic review they included 51 studies that, in total, described the outcome for almost half a million babies with known cord blood gas results. Most studies reported umbilical artery pH values but fewer data were available for venous pH or for base deficit. Fifteen studies reported long term outcomes with a median follow-up of five years. The quality of the studies varied, but quality did not seem to influence results on meta-regression. Further research is needed to refine the prognostic relevance of values in individual cases and to clarify the added value of base deficit, in addition to arterial pH.

Ultimately, given the findings of this study, we should aim to reduce the number of babies born with a low cord pH, without increasing unnecessary obstetric intervention. Hopefully this can be achieved by more hands-on input to labour ward care by fully trained obstetric specialists.[5]

The use of computerised intelligent systems to guide decision making by obstetricians and midwives might also help. The INFANT trial will assess whether outcome is improved by use of an intelligent system during labours in which cardiotocographic monitoring of the fetus has been undertaken. Cord artery pH less than 7.05 with base deficit greater than 12 mmol/l will be an important secondary outcome.[6]

In the meantime, the NICE recommendations that, "Paired cord blood gases do not need to be taken routinely. They should be taken when there has been concern about the baby either in labour or immediately following birth" remain valid.[4] US guidelines are most explicit and recommend taking paired samples from all babies born by caesarean section because of fetal compromise, low five minute Apgar scores, severe fetal growth restriction, abnormal fetal heart tracing, maternal thyroid disease, intrapartum fever, and all multiple births.[7] "Pairing" refers to sampling of both umbilical artery blood and vein blood. Different values confirm that the umbilical artery (blood direct from fetus) has been sampled separately from the more easily accessed vein (blood from placenta). If delayed cord clamping is practised, as it should be, as well as cord blood gas sampling, times should be carefully noted because the blood gas results will change with time.[8 9]

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RESEARCH, pp 1121, 1122, 1123

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Removing industrial *trans* fat from foods

A simple policy that will save lives

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As part of a 12 step manifesto to better public health, the UK Faculty of Public Health and Royal Society for Public Health proposed that consumption of *trans* fatty acids (TFAs) should be virtually eliminated in the United Kingdom by next year.[1] They noted that, "it has been proven that industrially-produced TFA can damage health," "there is no known safe level of consumption," and "banning TFA from foods is a relatively easy way to help protect the public."[1] Are these arguments sound?

TFAs are created when vegetable oils are partially hydrogenated to convert large numbers (typically 30-60%) of naturally occurring *cis* unsaturated double bonds into *trans* unsaturated double bonds. A high TFA content provides physical and chemical properties that are attractive to food manufacturers, including the creation of relatively inexpensive (compared with animal derived fats) solid or semi-solid fat. The process also destroys labile omega-3 acids (α-linolenic acid), and this reduces the propensity for fats to become rancid, increases shelf life, and optimises deep frying applications. Use of partially hydrogenated vegetable oils has increased since the 1950s because of these commercial advantages and since the 1960s because of public health recommendations to replace saturated fats (such as butter and lard) with alternatives.

Because mammals and most edible plants synthesise only *cis* double bonds, TFAs are rare in the natural human diet. Ruminant TFAs, found in meat and milk from cows, sheep, and goats and formed by the animal's gut flora, are the main natural source. Compared with industrial TFAs, ruminant TFAs contain some different isomers and are generally consumed in lower amounts (about 0.5% of total energy intake). At the low levels consumed, ruminant TFAs have no apparent major adverse health effects.[2 3] For these reasons, the 12 step manifesto sensibly focuses on eliminating industrially produced TFAs.

Total and industrial TFA consumption adversely affects several cardiovascular risk factors. In randomised trials, TFA consumption lowers high density lipoprotein cholesterol and raises low density lipoprotein cholesterol, triglycerides, the total cholesterol to high density lipoprotein cholesterol ratio, the apolipoprotein B to apolipoprotein A1 ratio, and Lp(a) lipoprotein.[2-4] TFAs may also promote systemic inflammation, endothelial dysfunction, insulin resistance, visceral adiposity, arrhythmias, and the development of diabetes.[2-4] Not surprisingly, TFA consumption is associated with a substantial risk of heart disease events, including myocardial infarction and death from coronary disease. This risk is far higher per calorie consumed than for any other dietary macronutrient, including saturated fat.[4]

Risk occurs even at low consumption. In developed nations, the average population consumption of TFAs is often 2-4% of total energy intake.[5] Major sources of industrial TFAs include baked goods, deep fried foods, packaged snacks, margarines, and shortening.[2] Paradoxically, consumption in developing nations may be even higher from cooking fat used at home or by street vendors, especially in lower income populations, because partially hydrogenated fats are often cheaper or even government subsidised in many regions.[6 7] Notably, average TFA consumption in any nation or region masks important subgroups of the population who are eating much more than the average, including people eating as much as 6-8% of total energy intake as TFAs.

Public campaigns, food labelling, and legislative policies may reduce TFA consumption. It recently became mandatory to include the TFA content on food labels in the United States and Canada, and this led some manufacturers to reduce or eliminate TFAs in some products.[8] However, many foods still contain industrial TFAs, especially in restaurants, schools, cafeterias, coffee shops, and bakeries, where food labels are not mandatory. Comprehensive education to encourage such businesses in New York City to voluntarily reduce the use of partially hydrogenated fats was unsuccessful.[9] Legislative strategies have been more successful than labelling or education. In both Denmark and New York City, legislation has effectively eliminated industrial TFAs; for example, in New York restaurants the prevalence of use of industrial TFAs has declined from 50% to less than 2%.[9 10]

What are the potential downsides to legislation? Concerns have been raised that such approaches might increase the use of saturated fats as a replacement; fail because of insufficient supply of appropriate replacement fats and oils; or reduce food availability, taste, or affordability. None of these concerns have been realised in Denmark or New York City. Reformulations that replace industrial TFAs with *cis* unsaturated fats would maximise health benefits; nevertheless, any reformulation removing partially hydrogenated fats—even if they were replaced with animal fats or tropical oils—would produce health benefits.[4] Furthermore, in practice,

manufacturers and restaurants generally remove TFAs from foods without corresponding increases in saturated fat.[8 9] Thus, we have no evidence that such legislation leads to harm from increased saturated fat. In addition, the experiences in Denmark and New York City show that adequate replacement fats and oils are available.[9 10] Seed developers, farmers, and oil processors seem to be responsive to changing demand. As demand for healthier fats and oils continues to increase, global supply and quality will probably continue to rise, while at the same time the partial hydrogenation of oils decreases. Finally, evidence suggests that mandated TFA reformulations do not appreciably alter prices, sales, taste, or availability of foods.[9 11] Indeed, the change is essentially invisible to consumers.

Because industrial TFAs are not part of our natural food supply, their regulation does not alter individual consumer choice, being similar to regulations that prohibit adulterated foods. With increasing supplies of alternatives, the commercial and cost advantages of partially hydrogenated oils are now small. Thus, removing industrial TFAs is one of the most straightforward public health strategies for rapid improvements in health. On the basis of current disease rates,[12] a strategy to reduce consumption of industrial TFAs by even 1% of total energy intake would be predicted to prevent 11 000 heart attacks and 7000 deaths annually in England alone.[2] A national, rather than regional, policy would also reduce the burden on manufacturers and restaurants and, importantly, protect all susceptible populations including children and socioeconomically disadvantaged subgroups. Action by the UK might also produce larger benefits by inspiring other developed and developing countries to take similar measures to protect their citizens' health.

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Takotsubo cardiomyopathy

An important differential diagnosis in patients with acute chest pain

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Takotsubo cardiomyopathy (also called stress induced cardiomyopathy, apical ballooning, or broken heart syndrome) was first described in Japan 20 years ago.[1] It is characterised by acute, reversible left ventricular dysfunction in a characteristic distribution, which does not correlate with the epicardial coronary artery blood supply. The left ventricular dysfunction occurs without obstructive coronary artery disease and usually resolves spontaneously over a period of weeks.

The characteristic appearances seen initially on contrast angiography are a ballooned apical segment and a hypercontractile basal portion of the left ventricle. The appearances are reminiscent of the design of the traditional fishing pot used in Japan to trap octopus, hence the descriptive term "tako-tsubo" cardiomyopathy.

Although this condition was initially considered rare, it could possibly be responsible for 1-2% of admissions for acute coronary syndrome in industrialised countries.[2] Apical left ventricular ballooning is the usual pattern, but involvement of the right ventricle or mid and basal left ventricular segments has been described.[3]

Takotsubo cardiomyopathy mainly affects postmenopausal women and is unusual in men. Symptoms seem to be triggered by psychological or physical stress (such as death of a family member, alcohol or drug withdrawal, acute somatic disorder, or abdominal surgery). An increased incidence was reported after an earthquake in Japan.[4] Typical ischaemic cardiac pain, with or without breathlessness, is the usual symptom, and on presentation the electrocardiogram may show ST elevation or negative T waves with QT prolongation. These ST segment changes may be widespread and can involve both anterior and inferior leads simultaneously. The blood biomarker troponin is usually slightly raised. The diagnosis of takotsubo cardiomyopathy requires coronary angiography to exclude obstructive coronary artery disease, and in the era of primary percutaneous coronary intervention, many of these patients will undergo immediate angiography for

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Endgames: Chest pain after emotional and physical upset (*BMJ* 2008;337:a107)

suspected acute myocardial infarction caused by coronary atheroma.

Treatment is supportive, and the prognosis is generally good because the dysfunction of the left ventricle usually resolves spontaneously over a couple of weeks. Treatment with β receptor blockers (in haemodynamically stable patients) and angiotensin converting enzyme inhibitors (in the absence of outflow tract obstruction) is usually recommended, although no randomised trials are available to support this. In a long term follow-up study of 41 Swiss patients at a mean follow-up of 675 days, none of the patients had died from a cardiac event and only two patients had a recurrence of symptoms.[2] However, severe left ventricular dysfunction can occur, and this can result in cardiogenic shock in about 4% of patients and ventricular fibrillation in 1.5%.[5] Treating cardiogenic shock as a result of takotsubo cardiomyopathy can be complex because intravenous catecholamines can cause paradoxical worsening of myocardial function. Introduction of an intra-aortic balloon pump is probably the treatment of choice, although administration of levosimendan (a non-catecholamine inotropic agent) has been proposed.[6]

The most common differential diagnosis is myocardial infarction caused by atheromatous coronary disease. Other causes of new electrocardiographic abnormalities (ST segment elevation or T wave inversion) should be excluded, and phaeochromocytoma or myocarditis should be considered before the diagnosis of takotsubo cardiomyopathy can be confirmed.[7] Similarities between takotsubo cardiomyopathy and the myocardial dysfunction described during intracranial bleeding or severe head trauma (neurocardiogenic stunning) suggest that these entities are probably manifestations of the same pathophysiological processes.[8]

The advent of sensitive troponin assays combined with increased use of early angiography probably explains the relatively recent description of this syndrome. Deferred investigation during the recovery phase of the left ventricle may result in the diagnosis being missed and perhaps an erroneous diagnosis of non-cardiac pain being made.

The pathophysiology of takotsubo cardiomyopathy seems to include endocrine, hormonal, neuropsychological, and microvascular factors. Reduced coronary flow reserve and signs of reversibly hypocontractile (hibernating) myocardium on biopsy specimens have been shown in small series of patients.[9 10] Major psychological stress seems to have a have a key role in the initiation of a cascade of biological events that cause temporary reductions in myocardial contractility. Patients with this condition have higher concentrations of circulating catecholamines than those with atherosclerotic acute myocardial infarction.[11] Relative oestrogen deficiency has been investigated as another cause, and takotsubo cardiomyopathy has been described after delivery in an oestrogen deficient woman with Turner's syndrome.[12] Future research into how reactions to stress interact with an altered hormonal status may reveal new insights into the link between the brain and the heart.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: (1) No financial support for the submitted work from anyone other than their employer; (2) No financial relationships with commercial entities that might have an interest in the submitted work; (3) No spouses, partners, or children with relationships with commercial entities that might have an interest in the submitted work; (4) No non-financial interests that may be relevant to the submitted work.

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CORRECTIONS AND CLARIFICATIONS

Should we consider a boycott of Israeli academic institutions? No

In a *Head to Head* debate published in July 2007 arguing against a boycott of Israeli academic institutions, Professor Michael Baum stated that it was "a lie" to suggest that the Israeli Medical Association (IMA) is complicit in the ill treatment of prisoners.[1] Although not mentioned in the debate by name, Dr Derek Summerfield has complained that this allegation refers to him because the statement in question referenced a letter from Dr Yoram Blachar,[2] then president of the IMA, in response to a letter from Dr Summerfield.[3]

We have sought clarification from Professor Baum, who states that he did not mean to imply that Dr Summerfield does not honestly believe that the IMA is complicit in such treatment. Professor Baum believes that Dr Summerfield is as sincere in his beliefs as he is in his own. We are happy to clarify the position, as requested by Dr Summerfield and Professor Baum.

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