Tamoxifen reduces recurrence and breast cancer mortality in women with early stage hormone sensitive breast cancer for up to 15 years. Beneficial effects of tamoxifen after surgery were also seen in women with weakly hormone sensitive breast cancer, defined as 10-19 fmol/mg of oestrogen receptor cytosol protein, but not in women with oestrogen receptor negative cancer.

Women with carcinoma in situ were excluded from this individual patient data meta-analysis of 20 trials, with more than 21,000 participating women. Comparison groups received observation or placebo. In most trials tamoxifen was given for five years, but this varied from two to 10 years across trials. Overall compliance was about 80%.

Improvements in survival were larger with longer treatment. The researchers have estimated that full compliance with five years of tamoxifen would reduce 15 year breast cancer mortality rates by at least a third, and probably more. This was largely independent of age, nodal status, tumour grade, tumour diameter, and chemotherapy use. Tamoxifen seemed safe in women younger than 55, but the risks of death from endometrial cancer or pulmonary embolus could be more than 1% in women over 55. In some trials tamoxifen showed the potential to reduce deaths from cardiovascular disease, but pooled analyses did not confirm this.

New and more sensitive assays for detecting low levels of oestrogen receptors would be useful, say the commentators (doi:10.1016/S0140-6736(11)61128-8), to identify more women who are candidates for treatment with tamoxifen but are currently being missed.

Lancet 2011; doi:10.1016/S0140-6736(11)60993-8

Rates of chronic conditions change by adolescence in children born extremely small

Children who weigh less than 1000 g at birth are prone to chronic diseases from early childhood, and this persists through adolescence. By the age of 14 years, however, one study found that rates of asthma and obesity become similar to those in children born at normal weight. The study followed 181 extremely low birthweight infants and 115 normal birthweight infants living in one US city, who were matched for sociodemographic position.

At ages 8 and 14, about three quarters of children born with extremely low birth weight had a chronic disease, as measured by the revised questionnaire for identifying children with chronic conditions. The corresponding figures for children born with normal weight were 37% and 47%, respectively. At age 14, children born with extremely low birth weight were almost three times as likely as children born at normal weight to have any chronic condition.

However, asthma remained constant—at 23%—in children born weighing less than 1000 g, whereas it increased from 8% at age 8 years to 17% at age 14 years in children born at normal weight. At age 14, the difference was no longer significant. In contrast, rates of obesity increased over the years in children born extremely small, from 12% at age 8 years to 19% at age 14 years, whereas rates remained relatively constant, at about 20%, in those born with normal weight.

JAMA 2011;306:394-401

How can rotavirus be controlled in India?

Natural infection with rotavirus has been shown to protect people from subsequent infections and severe diarrhoeal disease. Estimates have varied between studies though, from 46% to 100% protection.

In India, a birth cohort of 452 children living in urban slums was followed for the first three years of life. Children were visited twice a week. Stool samples, which were assayed for the presence of the virus, were taken biweekly and on alternate days during episodes of diarrhoea. Blood samples were taken twice each year and examined for seroconversion.

More than half of the children were infected with rotavirus by the time they were 6 months old. Only 30% of identified infections were deemed primary by the authors, the rest being reinfections. Of primary infections, only about 30% were asymptomatic.

Protection from further infections and moderate to severe disease increased as the number of previous infections increased and reached 79% after three infections. The researchers deemed the degree of protection to be lower than expected and recommended that vaccination strategies for India and similar settings may need to be modified by increasing the dose or number of doses of vaccine and considering earlier vaccination, such as neonatal or maternal immunisation. About half a million people are thought to die of rotavirus gastroenteritis globally each year.


HLA desensitution brings hope for some patients needing a kidney transplant

About a third of patients waiting for a kidney transplant have donor specific anti-HLA antibodies, which have always been thought to be a contraindication to transplantation because of increased risk of severe organ rejection and high rates of organ loss. These circulating anti-

Survival benefit of desensitisation
How third generation DNA sequencing helped control the Escherichia coli outbreak

By 22 July this year more than 4000 people in Germany had been infected with a new strain of Escherichia coli that produces the Shiga toxin; 50 of these people have died. The efforts of researchers worldwide have led to a quick realisation that the new strain is an unusual combination of two types of E coli bacteria.

Enterohaemorrhagic E coli, which produce the Shiga toxin, usually contain the enterocyte effacement pathogenicity island, which helps colonisation of the large intestine. However, the novel strain that caused the outbreak in Germany, and consequently spread to 15 other countries, was more similar to enterohaggregative E coli, which do not normally produce the toxin. Human cases of diarrhoeal disease with haemolytic-uraemic syndrome caused by enterohaggregative E coli that produce Shiga toxin have been described before, but only sporadically.

Third generation DNA sequencing, with emerging high throughput techniques, enable genomes to be sequenced within hours, rather than days to weeks. Both papers describe how open source genomic analysis, crowd sourcing, and a liberal approach to data release helped to control the threat to public health that was recently encountered in Germany.


TIME LINE OF THE OPEN SOURCE GENOMICS PROGRAMME

<table>
<thead>
<tr>
<th>Generation of sequencing technology</th>
<th>Sample received</th>
<th>2 kb and 6 kb Mate pair library</th>
<th>Pair end</th>
<th>Single end</th>
<th>500PE Library</th>
<th>Personal Genome Machine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Third</td>
<td>May 27</td>
<td>May 28</td>
<td>June 4</td>
<td>June 6</td>
<td>June 10</td>
<td>June 13</td>
</tr>
<tr>
<td>Second</td>
<td>May 29</td>
<td>May 30</td>
<td>June 11</td>
<td>June 13</td>
<td>June 14</td>
<td>June 15</td>
</tr>
<tr>
<td>First</td>
<td>May 31</td>
<td>June 1</td>
<td>June 15</td>
<td>June 18</td>
<td>June 16</td>
<td>June 18</td>
</tr>
</tbody>
</table>

Adapted from N Engl J Med 2011; doi:10.1056/NEJMoja1076643

Three germline mutations are linked to Barrett’s oesophagus

The incidence of Barrett’s oesophagus and oesophageal adenocarcinoma has risen 3 5-fold in Europe and the US in the past three decades. No one is sure why, but identifying cases early would save lives, because most cases of carcinoma are detected too late for treatment to be successful. A study identified three genes that might help with early diagnosis. All participants were white and of western and northern European descent.

The researchers first studied 21 pairs of siblings who were discordant for Barrett’s oesophagus and oesophageal adenocarcinoma, as well as 11 pairs of siblings who were discordant. The authors used the technique of genome wide mapping to identify three genes linked with the condition: MSR1, ASCC1, and CTHRC1.

Germline mutations in these genes were also confirmed in a separate cohort of 176 patients, matched for ancestry with 200 controls. A mutation in one of the three genes was found in 13 patients (11.2%) with Barrett’s oesophagus and oesophageal cancer but in none of the control participants. The most common were mutations in MSR1, with 7% (8/116) of the cases affected.

Yet another validation study confirmed the link with germline MSR1 and CTHRC1 in a separate series of 58 cases with Barrett’s oesophagus and oesophageal cancer.

JAMA 2011;306:410-9

People with HIV in Uganda have almost full life expectancy

In Europe and the US, people with HIV who start combination antiretroviral treatment at age 20 can expect to live for 49 more years. In Uganda, where life expectancy at birth is about 55 years, those who start combination treatment at age 20 can expect 26.7 (95% CI 25.0 to 28.4) additional years, and those who start treatment aged 35 can expect another 27.9 (26.7 to 29.1) years of life.

Similar to high income countries, survival with combination treatment was better in women than in men (27 v 44 deaths/1000 person years, respectively). People with higher CD4 cell counts at treatment onset lived longer. Mortality ranged from 67 deaths per 1000 person years in people with an initial CD4 cell count of fewer than 0.050×10⁹ cells/L to 19 deaths per 1000 person years in those with baseline a cell count of 0.250×10⁹ cells/L or more.

The study used data collected by the AIDS Support Organization (TASO), a public sector health system that provides clinical care, psychosocial support, and antiretroviral treatment to people with HIV at nearly four dozen clinics throughout Uganda, in both urban and rural settings.

Almost all patients were treated with older, more complicated, and more toxic regimens than are used in developed countries, says the linked editorial (p 265). It also notes that in the past few months we have learnt that some antiretrovirals can help halt the spread of HIV as well as treat those who are already affected. HIV can and must be controlled in Africa.

Ann Intern Med 2011;155:209-16

Cite this as: BMJ 2011;343:d4930

bodies are usually a consequence of a previous transplantation, pregnancy, or blood transfusion. Many such patients have a willing but incompatible live donor. It is unclear whether applying HLA desensitisation and proceeding with transplantation is better for these patients than waiting for a compatible donor.

An observational study from one US centre compared survival in 211 consecutive patients who underwent desensitisation with plasmapheresis and low dose intravenous immunoglobulin, with two matched control groups who either continued with dialysis only or eventually received an HLA compatible organ.

Over the 11 year study, survival was best in the desensitisation group. Of the patients who underwent desensitisation, 98% underwent transplantation and 80% were alive eight years later, compared with 30% in the dialysis only group and 49% in those who eventually received an HLA compatible organ.

Adverse events of desensitisation were mostly mild, although anaphylaxis and bleeding occurred and 11 of 211 patients (5%) underwent reoperation for bleeding. In addition, six patients in this group died of infection; although a direct link to desensitisation could not be established, such a connection merits further investigation, say the authors.