primary endpoint of death or dependency at 2 weeks (19·0% continue group *vs* 21·4% stop group: relative risk 0·86, 95% CI 0·65–1.14, p=0·30), despite a significantly lower blood pressure in those whose treatment was continued (13 mm Hg [95% CI 10–17] lower systolic and 8 mm Hg [95% CI 6–10] lower diastolic blood pressures). The COSSACS trial was underpowered because of early termination, but the ENOS trial will hopefully reliably assess whether blood-pressure-lowering drugs that have been prescribed before a stroke should be continued during the acute phase of stroke.

While awaiting the outcome of the large ongoing trials (table), SCAST's results suggest that actively lowering blood pressure within the first week of acute stroke is not beneficial.[4-6]

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I am a member of the Data Safety and Monitoring Committee of the INTERACT trial. I have received payment for consultancy work for: the Executive Committee, ROCKET-AF trial, Johnson & Johnson; the Executive Committee, BOREALIS trial, Sanofi-Aventis; and the Steering Committee, TRA 2P TIMI 50 trial, Schering Plough. I am on an advisory board for Pradaxa (dabigatran). I have received payments for lectures at scientific symposia sponsored by Sanofi-Aventis and Pfizer. My flight to attend the European Stroke Conference in Nice, 2008, was supported.

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# Cell-culture-derived influenza vaccine production

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In *The Lancet*, Noel Barrett and colleagues[1] report a randomised placebo-controlled trial of a trivalent influenza vaccine produced with viruses grown in Vero-cell culture. The vaccine proved to be highly efficacious in this field trial of more than 7000 adults aged 18–49 years. The results compared favourably with those from previous trials of the traditional egg-grown virus antigens in the same age group.[2]

The investigators pointed out several advantages of the tissue-culture substrate over those of embryonated eggs (panel). These advantages include availability and flexibility in use of tissue culture compared with the seasonality of use of hens' eggs which, for the large quantities needed, must be scheduled in advance. Egg-based production processes are susceptible to microbial contamination, which has delayed vaccine production at some manufacturing sites in recent years. Some human influenza viruses—especially subtype A H3N2—might be difficult to grow in eggs and yield the quantity needed for vaccine production. Avian viruses

that are a potential pandemic threat, such as subtype A H5N1, might be lethal for chick embryos.

The advantages of tissue-culture substrates allow a shorter production time between the annual determination of the vaccine's formula and the distribution of vaccine. The use of a tissue-culture substrate could shorten production time by 10 weeks,[3] which might be crucial in a pandemic alert. Furthermore, production of vaccine antigens in tissue culture provides a safer vaccine for individuals who are allergic to eggs.

Perhaps the most important advantage of tissue-culture-grown influenza antigens is the preservation of structure of the antibody-combining sites on the haemagglutinin.[4] Haemagglutinin is the most important surface antigen on the influenza virus, and protection is generally defined by the robustness of the antibody response to this antigen. Adaption of human influenza viruses to grow in the chick embryo alters the haemagglutinin antigen.[4,5] Animal studies suggest that the use of vaccine virus antigens grown in mammalian cells could enhance protection after challenge with the human virus.[5,6] Also, the immune response might be broader than that produced by egg-grown antigens, which allows the possibility of better protection against new variants of prevalent viruses.[5] The emergence of new variants has accelerated in recent years, especially for the influenza A H3N2 subtype. A shortened production time will allow more time to make decisions about which influenza strains should be included in the vaccine.

The Vero-cell culture has an advantage for licensure because other licensed vaccines, such as that for poliovirus, are produced in this substrate. However, the Vero-cell line is not the only one to consider for production of influenza vaccine. A large randomised trial in healthy adults, which compared MDCK-cell-culture-derived influenza virus vaccine with the standard egg-grown vaccine and placebo, was recently reported (MDCK=Madin-Darby canine kidney).[7] The MDCK vaccine was well tolerated and provided protection equal to that with the vaccine made with egg-grown viruses. Another cell line being considered for influenza vaccine production is E1-immortalised human retinal PER.C6 cells. PER.C6 cells are highly permissive for influenza viruses and can be efficiently transfected.[8] They are suitable for generation of influenza viruses by reverse genetics, which could decrease the risk of transmission of adventitious agents with the seed virus.[9]

***Panel:* Advantages of cell-culture-derived influenza vaccines**

- Permit growth of influenza viruses
- Available on short notice during any season
- Maintained in aseptic environment
- Reduce vaccine production time by about 10 weeks
- Might provide broader immunity to influenza variants
- Safe for individuals with allergy to eggs

What is lacking in the assessment of vaccines produced in tissue cultures? First, the manufacturers should have access to seed viruses that have not been passed in eggs. The alteration of the haemagglutinin antigen by egg adaption is not reversible; therefore seed viruses should be recovered and passed in tissue culture.[5] Reagents used for the measurement of the immune response should also not be produced from egg-adapted viruses.[10] For instance, the antibody titres for haemagglutinin inhibition reported by Barrett and co-workers were measured with egg-grown antigens. They found protection with titres as low as 1:15. If the titres had been measured with influenza antigens produced in mammalian tissue culture cells, the titres might have been higher. Also, the titres were measured 21 days after vaccination; the antibody response had probably not peaked at that time so the haemagglutinin inhibition titre at the time of natural challenge might have been higher than those recorded at 21 days.

The key to influenza control is the dependable availability of sufficient quantities of vaccine early in the season, preferably in August in the northern hemisphere. This schedule will allow more time for vaccine delivery and achievement of the Healthy People 2020 goals established in the USA of 80–90% coverage.[11] Tissue-culture substrates for vaccine production will facilitate progress. Safe vaccines which contain antigens that closely resemble the epidemic viruses will assure the likelihood of protection, and increase the demand for vaccine.

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# Mental health in southeast Asia

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The southeast Asia subregion (ASEAN: countries listed in the table) varies widely in populations, income, progress as reflected in the human development index,[1] and in resources in mental health systems.[1–3] Widespread poverty remains, and income inequality has substantially increased within countries. Rapid urbanisation, and social and cultural change, have generated new problems, particularly among the young.

Mental health has been a low priority. The main challenges are largely the product of lack of attention and investment. Where legislation and policies exist they are, at best, incompletely implemented, and efforts to modernise mental health systems have faced many obstacles.[4] In most of the countries, mental health spending is no more than 2% of the health budget, with 80–90% going to mental hospitals. There are massive workforce deficiencies; few consumer, carer, or other civil-society organisations with a focus on mental health advocacy; inadequate protection of the rights of people with mental illness; few efforts to promote mental health; little in the way of rehabilitation services or efforts to promote social and economic inclusion; and treatment services are concentrated in urban areas and often of poor quality, inaccessible, and unaffordable.

The direct consequences of neglect are many, including avoidable disability, impoverishment, and widespread human-rights abuses. Lack of attention to mental health, particularly in mothers, is hampering the achievement of several of the Millennium Development Goals. Most treatment is delivered through poorly resourced mental hospitals, a legacy of European colonisation, with all of the well-known deficiencies associated with such systems. A notable exception is Cambodia which, after the Pol Pot era, had no hospital, psychiatrists, or any other mental health professionals. The rebuilding of a mental health system there, from a primary care and community base, has been remarkable.[5] Although primary health care systems are generally well developed, capacity is limited to deliver mental health treatment and care through these systems, and to develop community-based services. In the many, particularly poor, provinces and districts with neither a mental hospital nor community services there is little or no access to treatment and care. Too often the only option left to families and communities is physical restraint and confinement of people with severe mental disorders.[6]

Reforms have focused on integration of mental health into general health care, with establishment of acute psychiatric units in general hospitals and efforts to incorporate mental health into primary care.[3,4,7,8] In Vietnam, the Doi Moi economic liberalisation programme in 1986 greatly affected health-sector reforms: the introduction of user fees at higher-level public health facilities put considerable pressure on a well-developed primary care system, private medical practice was legalised, and the drug industry was liberalised with deregulation of the retail trade in drugs.[3] Vietnam has had a community mental health programme, delivered through primary care,