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By contrast with the D:A:D report, Amy Cutrell and colleagues from GlaxoSmithKline (the makers of abacavir) report, in a Correspondence letter in today’s Lancet, that myocardial infarction did not increase in a summary of 54 pooled studies, 13 of which randomly assigned patients to receive abacavir. Although the low overall rates of myocardial infarction are somewhat reassuring, Cutrell and colleagues’ analysis is not powered to detect meaningful differences: it was based on only 18 myocardial infarctions and the limitations of summaries of pooled data for uncommon events in studies not designed to detect them are well known. Because coronary events were not adjudicated formally in these antiretroviral therapy efficacy studies, interpretation of the rates of “coronary artery disorders” is difficult. Available data on coronary heart disease from clinical trials, such as those included in the Cutrell report, should be submitted for peer review so their design and analyses can be described in detail and their conclusions fully interpreted.

The benefits of antiretroviral therapy were gleaned from a strong tradition of randomised trials. By contrast, most of the data on risks of coronary heart disease associated with antiretroviral therapy come from observational and short-term efficacy studies. Because patients are living longer with HIV and coronary heart disease is becoming a real risk to survival, studies lasting 24–48 weeks cannot guide what usually is lifelong therapy. Studies of antiretroviral efficacy should be of longer duration so their toxicities can be better understood. At the very least, long-term follow-up registries should be set up. Coronary events should be adjudicated in all randomised trials of antiretroviral efficacy, and well-validated surrogates of vascular outcomes should regularly be incorporated into efficacy studies. Recent randomised studies of antiretroviral therapy that prospectively investigated risk of coronary heart disease have challenged previously held beliefs and improved our understanding of the effects of antiretroviral therapy and HIV on vascular disease.

The power of the randomised efficacy trials should be used to investigate the coronary risks associated with antiretroviral therapy, so our dependence on observational cohorts and short-term efficacy studies as the only sources of information about the long-term risks of antiretroviral therapy can be reduced.

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JHS has received research funding from Bristol-Myers Squibb and honoraria from Abbott, Merck, and Pfizer for serving on scientific advisory boards; he has also given talks sponsored by pharmaceutical companies but does not accept personal remuneration and donates all honoraria directly to charity. JCS has received research funding and honoraria from GlaxoSmithKline, has received honoraria from Glaxo, has served as an advisor to Bristol-Myers Squibb, Pfizer, Merck, and Tibotec, receives research grants from Merck, Tibotec, and Theratechnologies, and serves on data safety and monitoring boards for Koronins and Achillion.

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Person-to-person transmission of influenza A (H5N1)

In February, 2004, in response to suggestions that limited person-to-person transmission of strain H5N1 of the influenza A virus might have occurred, the then Prime Minister of Thailand, said “the possibility of person-to-person transmission is 0·00001%”. Temperatures were running high, and any mention of person-to-person transmission of H5N1 was thought by some to be reckless. Although we have moved on, an air of tension still surrounds this disease, particularly in the corridors of power within the international health
Comment

and political communities, and apprehension remains about what the continued pandemic in poultry means for human health. Human H5N1 infections thankfully remain rare, but evidence has accumulated that in some circumstances H5N1 viruses are capable of limited person-to-person transmission.

Person-to-person transmission of H5N1 was first mooted after the 1997 Hong Kong outbreak, in which family members and at least two health workers might have been infected by contact with patients.\(^2,3\) Since then, one report of a family cluster concluded that person-to-person transmission was probable,\(^4\) and an additional four reports stated that it could not be ruled out in at least six families.\(^5-8\) In today’s *Lancet*, another convincing report of probable person-to-person transmission is published by researchers from China and the USA.\(^9\)

Transmission of avian influenza virus between mammals is not, however, restricted to H5N1 in human beings: H7N7 can also be transmitted from person to person,\(^10\) and there is evidence of transmission of H5N1 among other mammalian species.\(^11\) Given that the species barrier can be breached, the intriguing question is why the transmissibility of H5N1 among people remains so low?

Successfully crossing the species barrier is itself a step that might select viruses partly adapted to the new host and, once infected, the new host might select sub-populations of the virus adapted to the new environment. Apparent host-induced selection of a human-adapted H5N1 virus has been reported,\(^12\) but most sequence analyses of viruses isolated from sporadic and clustered cases show no substantial differences from the strains found in poultry. However, most of these analyses used viruses isolated from human specimens in cell cultures of animal origin, thus grown under different selective pressures from those in human respiratory tracts. Whether better adapted viral sub-populations exist during human infection is unknown, as is the diversity in virus populations in individual human beings or poultry. A possible lack of host-induced evolutionary pressure, disseminated viral replication and high viral loads in infected people,\(^13\) and the rarity of person-to-person transmission suggest that the infecting avian viruses might be already well adapted to the individual in which they find themselves, but not to the wider human population.

With the exception of occasional infection in health workers, all published incidents of possible or probable person-to-person transmission report transmission between genetically related individuals. Although this finding could be related to the intensity and intimacy of contact between family members, host genetic factors might also play a part in susceptibility to H5N1, and when we see limited person-to-person transmission we might be observing an interaction between two well matched sub-populations. Studying both within-host virus diversity and host genetic diversity might help to clarify the nature of the species barrier and the conditions necessary for widespread transmission between people. These studies are hard to do and need sustained, coordinated, and collaborative efforts, as in Wang and colleagues’ study,\(^9\) coupled with acceptance that person-to-person transmission of H5N1 can and does happen.

Whatever the underlying determinants, if we continue to experience widespread, uncontrolled outbreaks of H5N1 in poultry, the appearance of strains well adapted to human beings might be just a matter of time. In the meantime, all family contacts of a patient with probable or confirmed H5N1 should be given chemoprophylaxis and placed under surveillance. Personal protection and advice must be extended to the family members and health workers visiting and looking after patients in

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hospital. These steps rely on having systems capable of detecting cases and clusters early enough to start treatment and isolation, to identify and protect contacts, and to assess the extent of transmission.

Tension around emerging infections has led to often acrimonious and dispiriting debates about sharing of samples, international collaboration, and the roles of academic institutions, governments, and international agencies in fighting this common threat. Today's study is a superb piece of epidemiological work showing the benefit of a longstanding and trusting international collaboration that began during the severe acute respiratory syndrome epidemic. Such collaborations sustained over several years, centred in affected countries, and closely linked with WHO are our best chance of combating current and future threats to international health and ensuring that benefits are shared worldwide.

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Coronary artery disease in India: challenges and opportunities

Although cardiovascular disease is the leading cause of death worldwide, its epidemic shows remarkable geographic variation. While the mortality associated with cardiovascular disease seems to be declining in western Europe and North America,1 the burden of cardiovascular diseases in developing countries continues to rise and is expected to be a major cause of death in adults from low-income and middle-income countries worldwide.2 South Asians have a greater prevalence of coronary risk factors than the rest of the world, and coronary artery disease often manifests at an early age which creates unusual pressure on society and the economy.3

In today’s Lancet, Denis Xavier and colleagues4 describe the presentation, treatment, and outcome of more than 20 000 patients with acute coronary syndromes admitted to 89 hospitals across 50 cities in India. Patients in India were more likely to be younger and present with ST-elevation myocardial infarction than those in the registry data from developed countries. The use of lipid-lowering treatments, β blockers, and angiotensin-converting-enzyme inhibitors was low, and few patients had an invasive approach with coronary revascularisation. Substantial underutilisation of evidence-based treatments in poor people was seen, which largely explains the high morbidity and mortality in this group.

This registry is a major milestone, since it provides the first comprehensive view of the epidemic of acute coronary syndrome in India and helps to identify opportunities for improvement in care. As the Indian economy grows, there is a possibility for further increase in cardiovascular disease before we see a decline similar to that being witnessed in developed countries. Major risk factors of coronary artery disease are the same around the world. Tobacco use, dyslipidaemia, and hypertension are the main determinants of population attributable risk worldwide.5