Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

These two trials provide important information on the natural history of node-negative oestrogen-receptor-positive breast cancer, and offer insights into our ability to alter that natural history. Although node-negative patients are often referred to as low risk, it is clear from the 35% relapse rate in the placebo arm of NSABP B-14 that these patients are at significant risk for relapse. In that trial all patients benefited from tamoxifen use regardless of age or menopausal status, which translated into an overall survival benefit that was highest in the youngest cohort of patients. Less clear is which patients warrant chemotherapy in addition to tamoxifen. A survival benefit[5] has been seen with the addition of chemotherapy to tamoxifen in postmenopausal oestrogen-receptor-positive node-positive patients, but it is unclear whether this benefit can be extrapolated to all node-negative patients. NSABP B-20 showed significant benefits in terms of relapse-free survival in all age groups, but this resulted in a significant improvement in overall survival only in the youngest cohort. Clearly the expectations and limitations of chemotherapy must be discussed with patients, especially the elderly, because competing health concerns, such as heart disease, might outweigh the small potential benefit of adjuvant chemotherapy. Standard prognostic criteria,[6] and ongoing work with molecular profiling[7] may identify a subgroup of node-negative patients that has a particularly high risk for relapse and may benefit the most from adjuvant chemotherapy. This molecular profiling, with the current and planned Intergroup and Breast International Group trials, will provide insights into the effectiveness and indications for chemotherapy in node-negative and elderly patients, and is congruent with the statement made by Fisher et al that factors other than age and menopausal status must dictate systemic treatment.

Are these older trials relevant in the era of aromatase inhibitors? Recent adjuvant trials have suggested that aromatase inhibitors are effective both as initial therapy,[8] and after either 2–3 years[9] or 5 years[10] of tamoxifen. Both node-negative and node-positive patients benefit from these newer hormonal agents, and from the published data, one cannot identify a subgroup that should not be considered for treatment. The latest reports from NSABP provide reassurance about the long-term efficacy of tamoxifen, data that we do not yet have for the newer agents. One benefit of reviewing this follow-up data is a reiteration of the need for long-term follow-up and persistent reporting to ensure that efficacy is maintained and unanticipated toxicities are not uncovered. It is a reminder that cooperative groups are committed to a relentless re-analysis of the data. Adjuvant trials run by pharmaceutical companies must be held to the same standard.

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We declare that we have no conflict of interest.

1 Henderson IC, Berry DA, Demetri GD, et al. Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. *J Clin Oncol* 2003; **21:** 976–83.

2 Martin M, Pienkowski T, Mackey J, et al. TAC improves disease free survival and overall survival over FAC in node positive early breast cancer patients, BCIRG 001; 55 months follow-up. San Antonio Breast Cancer Symposium, San Antonio, Texas, 2003: abstr 43.

3 Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of intergroup trial C9741/cancer and leukemia group B trial 9741. *J Clin Oncol* 2003; **21:** 1431–39.

4 Bonadonna G, Brusamolino E, Valagussa P, et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. *N Engl J Med* 1976; **294:** 405–10.

5 Fisher B, Redmond C, Legault-Poisson S, et al. Postoperative chemotherapy and tamoxifen compared with tamoxifen alone in the treatment of positive-node breast cancer patients aged 50 years and older with tumors responsive to tamoxifen: results from the NSABP B-16. *J Clin Oncol* 1990; **8:** 1005.

6 Chia SK, Speers CH, Bryce CJ, et al. Ten-year outcomes in a population-based cohort of node-negative, lymphatic, and vascular invasion-negative early breast cancers without adjuvant systemic therapies. *J Clin Oncol* 2004; **22:** 1630–37.

7 Joensuu H, Isola J, Lundin M, et al. Amplification of erbB2 and erbB2 expression are superior to estrogen receptor status as risk factors for distant recurrence in pT1N0M0 breast cancer: a nationwide population-based study. *Clin Cancer Res* 2003; **9:** 923–30.

8 Baum M, Buzdar A, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer—results of the ATAC trial efficacy and safety update analyses. *Cancer* 2003; **98:** 1802–10.

9 Coomes RC, Hall E, Gibson LJ. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med* 2004; **350:** 1081–92.

10 Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med* 2003; **349:** 1793–802.

Chandipura virus: an emerging human pathogen?

In this issue of *The Lancet*, B Rao and colleagues describe an outbreak of acute encephalitis in north Andhra Pradesh and central-eastern Maharashtra, in southern India. The epidemic started at the beginning of the monsoon season in June, 2003, and lasted 3–4 months. In the state of Andhra Pradesh, 329 children aged between 9 months and 14 years developed encephalitis, and 183 died. The usual suspect would have been Japanese encephalitis virus. However, this virus normally emerges late in the monsoon season, and the disease in the Andhra Pradesh cases progressed faster than normal from an influenza-like illness to coma and death. The patients often complained of abdominal pains and vomiting, symptoms seldom associated with infection with Japanese encephalitis virus. Indian virologists turned their attention to other viral suspects, and were able to identify Chandipura virus as the culprit.

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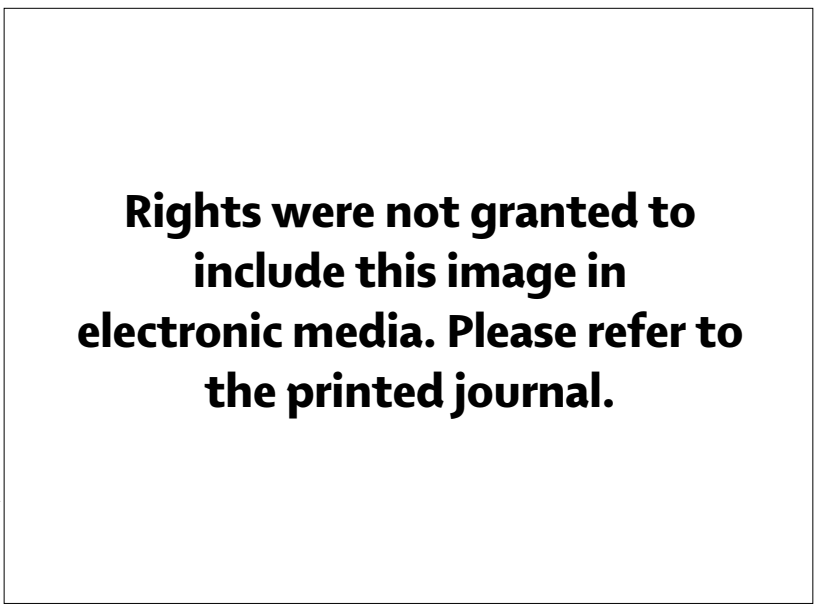

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Chandipura virus is a member of the Vesiculovirus genus of the family Rhabdoviridae. It was first isolated in 1965, from the blood of two adults with a febrile illness in a village in Nagpur County, Maharashtra State, India.[1] The only other instance when the virus was isolated in human beings was in 1980, in Madhya Pradesh, India, from a patient with acute encephalitis.[2] The likely vector of Chandipura virus is the female phlebotomine sandfly.[3] During the 2003 outbreak, Chandipura virus RNA was detected by PCR in sandflies collected around the house of a patient with encephalitis.

Since 1965, the virus has been reported in three adjoining states in central India: Madhya Pradesh, Maharashtra, and Andhra Pradesh. The virus has probably been endemic in this region for decades, and might have been responsible for several earlier outbreaks of encephalitis that have been recorded in India since 1954. However, the geographical distribution of the virus might extend well beyond India; it has also been detected in sandflies in Senegal and Nigeria.[4,5] Do not feel too bad if you have never heard of Chandipura virus before. Since the discovery of the virus in 1965, fewer than two articles a year have been published about it. In the year after the outbreak of severe acute respiratory syndrome (SARS) in 2003, more than 1800 articles were published on the SARS coronavirus. I doubt if the Chandipura virus outbreak in central India will be followed by a similar flurry of research activity. In the zoonotic animal virus farm, all viruses are equal, but some viruses are more equal than others. But, part of the explanation for the difference in research interests might be owing to the fact that Koch's postulates were fulfilled for the causal role of a novel coronavirus in the SARS epidemic, but not yet for the association of Chandipura virus with the outbreak of encephalitis in 2003.

The story of the first discovery of the Chandipura virus and its potential role in the 2003 outbreak can not be told without mentioning the National Institute of Virology (NIV) in Pune, India. This institute was established in 1952, under the auspices of the Rockefeller Foundation and the Indian Council of Medical Research, to investigate arthropod-borne viruses. The NIV is currently a WHO Collaborating Centre for arboviruses. Only when regional surveillance networks are closely cooperating with regional reference diagnostic laboratories can they function as effective early-warning beacons for emerging infections. The US Centers for Disease Control and Prevention cannot, and should not, function as the ultimate global reference laboratory. The threshold for sending samples to a small regional laboratory is lower than that for sending it to a far away and often culturally incongruent mammoth laboratory. Strengthening the regional diagnostic laboratory facilities in developing countries is an important global-health priority, and will result in a surveillance net with smaller meshes.

A lot has already been achieved, and the diagnosis of the current outbreak of viral encephalitis is a good example of a sentinel system that worked. However, much more remains to be done: in the infectious disease sphere, there are (and I paraphrase the US Secretary of Defense Donald Rumsfeld slightly out of context here) a lot of "known knowns; there are things we know we know. We also know there are known unknowns; that is to say we know there are some things we do not know. But there are also unknown unknowns—the ones we don't know we don't know." The 2003 encephalitis outbreak in India taught us that the previously unknown Chandipura virus joins the seemingly ever-growing list of the known important human pathogens. I bet there are still a lot of unknown unknown infectious diseases awaiting us.

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I declare that I have no conflict of interest.

1 Bhatt PV, Rodriguez FM. Chadipura: a new arbovirus isolated in ` India from patients with febrile illness. *Indian J Med Res* 1967; **55:** 1295–305.
2 Rodrigues JJ, Singh PB, Dave DS, et al. Isolation of Chandipura virus from the blood in acute encephalopathy syndrome. *Indian J Med Res*. 1983; **77:** 303–07.
3 Dhanda V, Rodriguez FM, Ghosh SN. Isolation of Chandipura virus from sand flies in Aurangabad. *Indian J Med Res* 1970; **58:** 179–80.
4 Fontenille D, Traore–Lamizana M, Trouillet V, et al. First isolations of arboviruses from Phlebotomine sand flies in West Africa. *Am J Trop Med Hyg* 1994; **50:** 570–74.
5 Clewley JP, Bishop DH, Kang CY, et al. Oligonucleotide fingerprints of RNA species obtained from rhabdoviruses belonging to the vesicular stomatitis virus subgroup. *J Virol* 1977; **23:** 152–66.