

an effective public health approach to contain the epidemic of NCD. However, we need to review a few issues. First, is BMI an appropriate indicator of obesity in Asians? Interpretation of BMI grading in relation to risk differs for different populations. Since BMI essentially estimates both fat and fat-free mass (bone, muscles and body water) it fails to distinguish between fat and fat-free mass.⁴ Moreover, some characteristics of Asians such as short stature, stunting of growth and malnutrition may alter appropriateness of assessing the relationship between height, weight and body composition.³ Dudeja *et al.*⁵ studied 123 subjects and found that native north Indians have a higher proportion of body fat but their BMI may not be high. Some studies suggest that it is the distribution of fat, i.e. subcutaneous fat in the abdominal region, that has a major impact on metabolic variables.^{2,3,6}

A consensus statement was proposed on the diagnosis of obesity, abdominal obesity and metabolic syndrome in Asian Indians after consultations with experts from various regions of India belonging to different medical disciplines.⁷ This statement gives equal importance to BMI and waist circumference for population- and clinic-based metabolic and cardiovascular risk stratification. The National Family Health Survey (NFHS-3) of 2005–06 reported 57% of men and 52% of women belonging to the so-called ‘normal’ range of BMI (18.5–24.9 kg/m²). Putting this ‘normal’ range in relation to the finding of this study that BMI in the low–normal range (18.5–22.5 kg/m²) has an increased risk of death, would invite enormous public health reaction. This seemingly innocuous statement would translate into a death sentence for people who are still in the ‘normal’ range. At the same time, overlooking this issue without due assessment may be an act of omission at the policy and public health levels.

Based on the experience from pilot studies in 10 states in India, a national programme for the prevention and control of diabetes, cardiovascular disease (CVD) and stroke is expected to be launched by the Ministry of Health and Family Welfare, Government of India.⁸ We propose the creation of a separate cadre of health worker/community-level worker to look after all the ongoing NCD programmes at the grassroots level. From the feasibility point of view, it will be apt to recommend that these grassroots-level workers may measure waist circumference (WC) in a selected section of the population for risk identification.

The aim of the PSC study was to examine the relevance of BMI to cause-specific mortality ≥ 5 years after recruitment to those studies. The PSC study reported that BMI is associated with increased total mortality in both men and women, and in all age strata from 35 to 89 years. The findings of the PSC study are important. However, formulation of BMI-based mortality risk for India needs to be informed by geographically representative community-based studies across the country, including follow up studies or the morbidity and mortality outcomes. We believe that measuring BMI is more feasible at a health facility (sub-centre, primary health centre, community health centre and district hospital) and WC at the community level. Such data generated from India would better inform policy-makers and thus help strategically improve the implementation of the NCD programme.

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Neuraminidase inhibitors for influenza in healthy adults: What we don't know

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and treating influenza in healthy adults: Systematic review and meta-analysis. *BMJ* 2009;**339**:b5106.

SUMMARY

The authors systematically reviewed and did a meta-analysis of studies that evaluated the efficacy of neuraminidase inhibitors (inhaled zanamavir and oral oseltamivir) for treatment of laboratory-proven cases of influenza, and pre- and post-exposure prophylaxis. Four studies which assessed the efficacy for preventing influenza were included in the study. Two of the 4 studies used oral oseltamivir 75 mg daily while 2 studies used inhaled zanamavir 10 mg daily. The authors found that the current evidence neither supports nor refutes the use of neuraminidase inhibitors for the prophylaxis of influenza (risk ratio 1.28 [CI: 0.45–3.66] for oseltamivir and 1.51 [0.77–2.95]

for zanamavir). It was also observed that both oseltamivir and zanamavir were efficacious in preventing symptomatic laboratory-proven cases of influenza. In the 4 studies, which evaluated the prophylactic use of neuraminidase inhibitors in household contacts of proven cases of influenza, both oseltamivir and zanamavir provided protective effect (risk ratios range: 0.16–0.42).

Twelve studies which evaluated the benefits of neuraminidase inhibitors for therapeutic purpose were included in the study. Both oseltamivir (hazard ratio 1.24, CI: 1.13–1.36) and zanamavir (hazard ratio 1.20, CI: 1.06–1.35) reduced the duration of illness by 1 day. However, data on the prevention of complications of influenza were lacking. Although a previous meta-analysis¹ has shown benefit in reduction of complications, the authors of this meta-analysis excluded that study due to non-availability of detailed data from studies included in that meta-analysis. The exact role of neuraminidase inhibitors in the 2009 H1N1 epidemic has not yet been evaluated in clinical studies.

Before this meta-analysis, the safety data of neuraminidase inhibitors were limited. Nausea was reported with use of oseltamivir (odds ratio 1.79, CI: 1.1–2.93) and was higher with the dose of 150 mg daily compared with lower doses (odds ratio 2.29, CI: 1.34–3.92). Neuropsychiatric events were observed at a rate of 0.5% with oseltamivir in prospective clinical trials. Retrospective studies suggest an incidence of 20–27 neuropsychiatric adverse events per 1000 adults at 14 days and 30–40 neuropsychiatric adverse events per 1000 adults at 30 days. No serious adverse events were noted with zanamavir in clinical trials.

COMMENT

Till recently, neuraminidase inhibitors were accepted as a therapeutic modality and incorporated into various national and international guidelines. Use of neuraminidase inhibitors for treatment of patients with influenza who have other risk factors such as extremes of age, pregnancy, pre-existing co-morbid conditions and immune-suppression is well accepted and non-controversial.¹ Similarly, they have been used for prophylactic purposes. The current study strengthens the practice of chemoprophylaxis in household contacts. Recent recommendations suggest the use of neuraminidase inhibitors in high risk individuals with recent contact and close follow up for otherwise healthy individuals.¹

In this study the use of neuraminidase inhibitors for treatment of influenza in healthy adults was also evaluated. The results suggest a modest reduction of hospital stay by 1 day. The efficacy of neuraminidase inhibitors in preventing complications of influenza was not proven in this meta-analysis and the results neither support nor refute this notion. More importantly, the results are in contrast with the findings of Kaiser *et al.*,² who had concluded that treatment with oseltamivir in influenza illness reduces lower respiratory tract complications (LRTC) by 55% (4.6% v. 10.3% with placebo; $p < 0.001$), antibiotic use by 26% (14% v. 19.1% with placebo; $p < 0.001$), and hospitalization by 59% (0.7% v. 1.7%; $p = 0.02$) in both healthy adults as well as adults with co-morbid conditions.¹ The study by Kaiser *et al.* has been the basis for many national guidelines and healthcare policies.³ Many countries have made huge stockpiles of oseltamivir costing billions of dollars for epidemic preparedness in view of H5N1 outbreaks and 2009 H1N1 influenza pandemic.⁴ On the request of Dr Hiyashi, a Japanese paediatrician who was not convinced by the meta-analysis conducted by Kaiser *et al.* and the Cochrane review which included the study by Kaiser *et al.*, the Cochrane group conducted the current meta-analysis.⁵ The contrasting results of the current study and the study by Kaiser *et al.* have opened up a Pandora's box and left many questions unanswered pertaining to the conduct and publishing of studies,

regulations regarding availability of data pertaining to drug trials and public health planning.

The study by Kaiser *et al.* included data from 10 studies, all of which were funded by Roche pharmaceuticals and were authored by Roche employees and paid consultants.⁶ Only 2 of the 10 studies were published in peer-reviewed journals. The 8 unpublished studies included 2691 of 3564 patients.^{2,6} Further, in the study by Kaiser *et al.*, the incidence of LRTC was much higher than the incidence one encounters in clinical practice.² What is even more disturbing than the methodology and results of the study is the stance taken by Roche pharmaceuticals. They were not ready to provide complete data for all unpublished studies, neither the authors of the studies could provide the same. This led to an investigation by *BMJ* and Channel 4, which brought out some startling facts and raised more questions on the conduct of the studies and the handling of data by Roche.⁵ Roche have tried to reply and justify their act of not providing the raw data to the practice prevalent at that time, which did not mandate the study protocols and reports to be made public, as it is now.⁷ However, they are silent on inclusion of non-published data in the meta-analysis, where guidelines to the contrary have long been available.⁸ Even if their objection about involvement of a commercial television channel in the entire episode may have some merit, the questions raised about the validity of the meta-analysis conducted by Kaiser *et al.* and the equivocal results of the current meta-analysis, benefits of neuraminidase inhibitors for therapeutic use in otherwise healthy adults stands to further scrutiny and need to be confirmed in an independent review of the raw data of studies conducted by Roche and well designed randomized controlled trials in the future.

The serious adverse events of neuraminidase inhibitors have not been studied in detail till now. The current study suggests 20–27 neuropsychiatric adverse events per 1000 adults at 14 days and 30–40 neuropsychiatric adverse events per 1000 adults at 30 days. With strong evidence lacking for the therapeutic use of neuraminidase inhibitors in healthy adults and emerging data of serious adverse events, one needs to re-evaluate the benefits and risks of the use of neuraminidase inhibitors. In view of the current pandemic of 2009 H1N1 where large population of healthy adults are at risk of acquiring influenza and a low incidence of severe influenza (LRTC) with 2009 H1N1 in healthy adults, the findings of the current study have great importance. The US Food and Drug Administration (FDA) and WHO guidelines do not support the use of neuraminidase inhibitors for therapeutic use in healthy adults with mild disease.^{2,9} It needs to be seen whether these new findings lead to any further amendments in healthcare policies and, more important, any changes in the principles which guide the role of pharmaceutical companies in the conduct of clinical trials, analysis of data and preparation of manuscript. It is important to stress that trial data should be available for public scrutiny which would provide credibility both to the clinical trials and healthcare policies based on these trials.

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