Clustering of chronic non-communicable disease risk factors among selected Asian populations: levels and determinants

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Background: The major chronic non-communicable diseases (NCDs) operate through a cluster of common risk factors, whose presence or absence determines not only the occurrence and severity of the disease, but also informs treatment approaches. Primary prevention based on mitigation of these common risk factors through population-based programmes is the most cost-effective approach to contain the emerging epidemic of chronic NCDs.
Objectives: This study was conducted to explore the extent of risk factors clustering for the major chronic NCDs and its determinants in nine INDEPTH Health and Demographic Surveillance System (HDSS) sites of five Asian countries.
Design: Data originated from a multi-site chronic NCD risk factor prevalence survey conducted in 2005. This cross-sectional survey used a standardised questionnaire developed by the WHO to collect core data on common risk factors such as tobacco use, intake of fruits and vegetables, physical inactivity, blood pressure levels, and body mass index. Respondents included randomly selected sample of adults (25–64 years) living in nine rural HDSS sites in Bangladesh, India, Indonesia, Thailand, and Vietnam.
Results: Findings revealed a substantial proportion (>70%) of these largely rural populations having three or more risk factors for chronic NCDs. Chronic NCD risk factors clustering was associated with increasing age, being male, and higher educational achievements. Differences were noted among the different sites, both between and within country.
Conclusions: Since there is an extensive clustering of risk factors for the chronic NCDs in the populations studied, the interventions also need to be based on a comprehensive approach rather than on a single factor to forestall its cumulative effects which occur over time. This can work best if it is integrated within the primary health care system and the HDSS can be an invaluable epidemiological resource in this endeavor.

Keywords: *chronic NCDs*; *risk factors surveillance*; *clustering*; *INDEPTH*; *Asia*; *WHO STEPS*

Chronic non-communicable diseases (NCDs) such as heart disease and stroke, diabetes mellitus, cancer, and chronic respiratory diseases account for approximately 60% of total mortality in the world, with around 80% of these deaths occurring in low and middle-income countries (1). According to a recent projection, seven out of every 10 deaths in low-income countries will be from chronic NCDs by 2020 (2), and

poses a serious challenge to the developing countries (3). WHO have been advocating policy makers to develop efficient strategies to halt 'tomorrow's pandemic' of the chronic NCDs (4, 5).

The risk factors underlying the major chronic NCDs are well documented and are relatively few in number (6). These include tobacco and alcohol consumption, unhealthy diet (low in fruits and vegetables and high in salt, fat, and sugar), physical inactivity (sedentary lifestyle), and raised blood pressure (BP) which may explain 75% of these chronic NCD conditions (2, 7). Evidence shows that the major chronic NCDs operate through a cluster of common risk factors, whose presence or absence determines the occurrence and severity of the disease (8–10).

The burden of NCDs is also increasing in South Asia. Almost half of all deaths in Asia are now attributable to NCDs, accounting for 47% of global burden of disease (11). In contrast to conventional wisdom, poverty has been found to be a predictor of chronic NCDs in 'low income' countries (12, 13) like the 'high income' countries (14, 15). Evidence is now emerging on linkage of low birth weight to incidence of chronic NCDs in later life (16), intrauterine origin of chronic NCDs (17), and under-nutrition in fetal life giving rise to the development of chronic NCDs in adult life (18). The increased prevalence of NCDs in these countries is linked to the rapid urbanisation and increasing globalisation of the food, tobacco, and alcohol industries (10).

There is lack of comprehensive data on NCD risk factors and its clustering in the Asian countries. Some small-scale studies have been done in India in industrial settings (19), in urban slums (20), and in urban, per-urban, and rural areas for specific disease and risk factors (21, 22). Similar studies on risk factors for specific disease/area have also been done in Vietnam (23), Indonesia (24), and Bangladesh (25, 26). However, these studies did not address the risk factors from a generic approach which is essential for designing a comprehensive preventive intervention.

This paper aims to fill in this knowledge gap and explore the extent of risk factors clustering for the major chronic NCDs and its determinants in nine Health and Demographic Surveillance System (HDSS) sites of five Asian countries, which are members of the IN-DEPTH Network (please see below). This information will have important policy implications for identifying potential population groups at risk and designing targeted cost-effective interventions both at the population level and at the individual level, in order to reduce burden of chronic NCDs within the shortest possible time.

Materials and methods

Data source

This cross-sectional study used pooled dataset from nine HDSS sites in five Asian countries namely Matlab, Mirsarai, Abhoynagar and WATCH (Bangladesh), Kanchanaburi (Thailand), Filabavi and Chililab (Vietnam), Vadu (India), and Purworejo (Indonesia). The choice of these HDSS sites (and countries) happens to arise from their affiliation to the INDEPTH, a network of HDSS sites in developing countries (http://www.indepth-network.org). Its purpose is to monitor population dynamics and to test and evaluate various health interventions to influence policy and practice, and improve population health. All these rural sites are conveniently located in particular geographical areas of the respective countries and as such is not representative of the entire country. However, these provide an indication of the current situation prevailing in these countries. These low (Bangladesh, Vietnam, India) and middle income (Thailand, Indonesia) countries are experiencing different stages of demographic, economic, and epidemiological transitions.

Sampling and survey

In each site, a sample was drawn following the WHO STEPS methodology (27), which included a minimum of 250 individuals in each 10 years age group (25–64 years) for each sex to a total of 1,000 males and 1,000 females. From the HDSS sampling frame, a stratified random sampling technique was used to draw samples in each age and sex group. In STEP 1, an assessment of chronic NCDs risk factors (such as tobacco and alcohol consumption, physical inactivity, fruit and vegetable intake) was undertaken by questionnaire. Data on core items of selected risk factors were collected through face-to-face interview during household visits by trained interviewers using a pre-tested local version of the WHO STEPS questionnaire. In addition, because of the widespread practice of chewing tobacco in most of the HDSS, expanded questions on this item were also included as an option. In STEP 2, weight, height, and BP measurements were taken using standardised instruments and protocols.

To ensure uniform and standard method of data collection across sites, the principal investigators initially met and agreed on standard study protocol and data collection instruments and later, training was organised by them at the site levels. BP was measured using digital device (Omron M4-I, Omron Healthcare, Europe BV, Hoofddorp, the Netherlands). BP was measured at the right arm at heart level after a period of 10 minutes of rest. Out of three measurements, the average of the last two readings were used. Raised BP was defined as systolic BP (sbp) ≥ 140 mmHg and diastolic BP (dbp) ≥ 90 mmHg or under any anti-hypertensive drug medication.

Weight and height were measured in light-weight clothing and standing barefoot on instruments placed on a flat surface. Weight was measured to the nearest 10 grams using an electronic scale (Seca Gmbh, Hamburgh, Germany) and height was measured to the nearest 0.1 cm using a portable stadiometer. Body mass index (BMI) was calculated as weight in kg divided by height in metre squared. All measuring instruments were procured centrally and distributed to the respective sites. The details of the study design, other measurements, and the process of quality control in the survey are described elsewhere (28).

Data analysis

A standardised data entry programme using EPIDATA software was used in each site for data entry to ensure uniformity. Data were analysed using STATA version 10. All analyses were weighted by the age and sex structure of the HDSS population and categorisation of the variables followed the WHO STEPS standard format (28). The choice of the variables included in the model was based on the WHO STEPS summary table for surveillance sites (http://www.who.int/chp/steps). The prevalence of risk factors clustering at different sites was compared and multivariate logistic regression was undertaken to explore the association between clustering of risk factors and sociodemographic variables of interest. Significance level $p < 0.05$ was used.

Ethical issues

The multi-site study protocol was approved by the Scientific Board of the INDEPTH Network and also passed through the usual institutional review process at the different study sites. Informed consent (both verbal and written) was taken from every respondent before including him/her in the study. A commitment to confidentiality was ensured in the consent forms and training exercise. Any participant with high BP or other disease was referred to appropriate facilities for investigation and treatment.

Results

A total of 18,494 men and women were included into the study representing an overall 98% response rate. Detailed information on their socioeconomic characteristics, which were extracted from the overall database, was reported in the first paper in this supplement (28). Among the behavioural risk factors, current daily smoker of tobacco was high in men (>50%) in all sites except Vadu and Abhoynagar (Table 1). Reported prevalence of physical inactivity was highest in Filabavi (58%) followed by Vadu (53%) and Matlab (51%) with gender difference disfavoring women in all sites except those from Vietnam (Table 1). Except in Chililab and Kanchanaburi, more

than 80% of the respondents in other sites reported low consumption of fruits and vegetables.

Kanchanaburi (28%), Purworejo (24%), and Vadu (24%) reported greater prevalence of raised BP (sbp $\geq$ 140 mmHg and dbp $\geq$90 mmHg) compared to other sites. Prevalence was higher in men than in women except in the sites from Bangladesh (Table 1). Over-weight (BMI $\geq$25) was greater in Kanchanaburi (35%) and Purworejo (18%) than other sites, with women being heavier than men in all HDSS except in Vadu and Chililab (Table 1).

Table 2 presents the distribution of risk factors clustering (three or more) by age group and sex among the different sites. The proportion of respondents without any of the above behavioural and biological risk factors was negligible, with the exception of Chililab in Vietnam where around 20% reported none of the major risk factors. Higher prevalence of clustering (>20%) was observed in Kanchanaburi and Mirsarai for men and in all sites except Abhoynagar, WATCH, and Chililab for women. The level of clustering among women was higher than men overall, and especially in the two sites in Vietnam.

Table 3 presents results from multivariate logistic regression analysis of predictors of risk factors clustering ($\geq$3 risk factors) among the different sites. The probability increased significantly with age in all sites, especially in the elderly age group (55–64 years); the probability was more than three times higher in sites from India, Indonesia, and partly Bangladesh (Mirsarai and Abhoynagar) compared to other sites. The probability was also higher among men compared to women except Mirsarai and Abhoynagar. Sites from Vietnam showed a very large difference (nine times more in men compared to women). Again, the higher the education level, the greater the probability of risk factors clustering, except sites from Vietnam; the probability was significant for sites from Matlab, Vadu, Filabavi, and Purworejo.

In summary, chronic NCDs risk factors clustering was predicted by age (probability increasing with age), sex (probability increased if male), and education (probability increasing with higher educational level).

Discussions

Clustering of risk factors, whether behavioural or biological, is associated with the occurrence of the major chronic NCDs (8, 19). As such, it is important to identify the groups at risk to design appropriate intervention measures. This paper explores this phenomenon using risk factor prevalence data from nine HDSS sites in five Asian countries affiliated with INDEPTH. The findings revealed widespread use of tobacco in men, low consumption of fruits and vegetables, low physical activity levels in women, and a high proportion of the population with raised BP (sbp $\geq$140 mmHg and

Table 1. Prevalence of five major behavioural and biological risk factors (95% CI) in nine Asian HDSS sites, men and women 25–64 years

	Bangladesh				India	Vietnam		Indonesia	Thailand
	Matlab	Mirsarai	Abhoynagar	WATCH	Vadu	Chililab	Filabavi	Purworejo	Kanchanaburi
Men									
Current daily smoker	52.5 (49.3–55.7)	62.6 (59.5–65.7)	46.6 (43.4–49.8)	59.7 (56.4–63.0)	7.1 (5.5–8.6)	51.5 (48.4–54.6)	59.5 (56.3–62.7)	62.7 (59.7–65.8)	53.4 (50.3–56.5)
Less than five servings of fruits and vegetables/day	88.2 (86.1–90.3)	94.5 (93.0–96.0)	88.6 (86.5–90.6)	100.0	100.0	63.5 (60.5–66.5)	87.0 (84.7–89.2)	93.4 (91.9–95)	76 (73.3–78.7)
Low level of physical activity	34.5 (31.5–37.6)	24.3 (21.5–27.1)	19.2 (16.6–21.8)	11.7 (9.5–13.9)	51.7 (48.5–54.8)	15.4 (13.2–17.6)	63.0 (59.8–66.1)	12.3 (10.2–14.4)	14.6 (12.4–16.8)
Overweight (BMI ≥25 kg/m^2)	10.2 (8.2–12.2)	10.0 (8.1–12.0)	9.2 (7.4–11.1)	5.2 (3.7–6.7)	16.7 (14.3–19.1)	6.7 (5.2–8.2)	1.8 (0.9–2.6)	10.0 (8.0–11.9)	24 (21.3–26.7)
Raised blood pressure	12.5 (10.4–14.5)	20.3 (17.8–22.9)	13.3 (11.3–15.4)	7.4 (5.8–9.0)	25.5 (22.7–28.2)	22.4 (19.9–24.9)	20.2 (17.6–22.7)	24.1 (21.4–26.7)	32.1 (29.2–35)
Women									
Current daily smoker	0.8 (0.3–1.3)	0.3 (0.0–0.6)	1.4 (0.6–2.1)	2.7 (1.8–3.6)	0.1 (−0.1–0.3)	0.4 (0.0–0.7)	0.5 (0.0–0.9)	1.4 (0.7–2.1)	6.3 (4.9–7.8)
Less than five servings of fruits and vegetables/day	90.4 (88.4–92.4)	97.4 (96.3–98.4)	96.6 (95.3–97.8)	100.0	99.8 (99.6–100.1)	57.5 (54.4–60.5)	87.5 (85.3–89.6)	89.5 (87.6–91.5)	72.6 (69.9–75.4)
Low level of physical activity	64.0 (60.9–67.2)	64.8 (61.7–67.9)	38.2 (35.0–41.4)	21.2 (18.4–24.0)	54.2 (51.1–57.4)	10.7 (8.8–12.6)	52.8 (49.6–56.0)	25.6 (22.8–28.4)	24.1 (21.5–26.8)
Overweight (BMI ≥25 kg/m^2)	13.9 (11.6–16.3)	12.7 (10.5–14.8)	13.8 (11.5–16.0)	8.2 (6.3–10.2)	12.0 (10.0–14.0)	5.9 (4.5–7.3)	1.9 (1.0–2.7)	24.6 (21.7–27.4)	43.5 (40.4–46.5)
Raised blood pressure	21.0 (18.4–23.5)	27.4 (24.6–30.3)	19.8 (17.3–22.3)	11.2 (9.1–13.2)	21.6 (19.1–24.1)	14.7 (12.6–16.7)	10.3 (8.5–12.1)	24.0 (21.3–26.8)	24 (21.4–26.5)

Clustering of risk factors in rural Asian INDEPTH HDSS

Table 2. Prevalence of risk factors clustering (95% CI) in nine Asian HDSS sites, by gender

	Bangladesh				India	Vietnam		Indonesia	Thailand
	Matlab	Mirsarai	Abhoynagar	WATCH	Vadu	Chililab	Filabavi	Purworejo	Kanchanaburi
Men									
None of the above risk factors	2.5 (1.4–3.5)	0.1 (–0.1–0.3)	1.7 (0.8–2.6)	0 (0–0)	0 (0–0)	30.2 (27.3–33.0)	5.3 (3.9–6.8)	3.9 (2.6–5.2)	10 (8.1–11.9)
With three or more of the above risk factors, aged 25–44 years	15.6 (12.4–18.8)	17.2 (13.8–20.5)	11.3 (8.5–14.2)	5.1 (3.1–7.1)	12.5 (9.6–15.4)	0.6 (–0.1–1.2)	2.6 (1.2–4.0)	14.5 (11.1–17.8)	15.4 (12.3–18.5)
With three or more of the above risk factors, aged 45–64 years	25.9 (22.1–29.8)	35.9 (31.6–40.2)	18.9 (15.5–22.4)	9.6 (7.0–12.2)	26.7 (22.8–30.5)	3.3 (1.8–4.8)	13.0 (10–15.9)	16.7 (13.3–20.0)	27.3 (23.5–31.1)
With three or more of the above risk factors, aged 25–64 years	18.9 (16.4–21.4)	24.0 (21.3–26.7)	14.1 (11.9–16.3)	6.4 (4.8–8.0)	17.7 (15.4–20.0)	1.7 (1.0–2.4)	6.6 (5.2–8.0)	15.5 (13.1–17.9)	20.2 (17.8–22.6)
Women									
None of the above risk factors	3.4 (2.2–4.6)	0.8 (0.2–1.4)	2.4 (1.4–3.4)	0 (0–0)	0 (0–0)	11.2 (9.2–13.2)	1.4 (0.6–2.2)	1.3 (0.6–2)	5.4 (3.9–6.8)
With three or more of the above risk factors, aged 25–44 years	23.0 (19.3–26.7)	23.6 (19.9–27.4)	14.6 (11.4–17.7)	9.2 (6.6–11.8)	23.1 (19.5–26.7)	14.5 (11.5–17.5)	39.8 (35.5–44.1)	16.3 (13.0–19.7)	23.8 (20.1–27.5)
With three or more of the above risk factors, aged 45–64 years	29.7 (25.7–33.6)	32.9 (28.8–37.1)	19.3 (15.8–22.9)	16.8 (13.4–20.2)	27.7 (23.7–31.8)	17.1 (13.8–20.5)	45.1 (40.4–49.9)	29.2 (25.1–33.2)	34.4 (30.2–38.6)
With three or more of the above risk factors, aged 25–64 years	25.3 (22.6–28.1)	27.3 (24.4–30.1)	16.4 (14.1–18.8)	11.8 (9.7–13.8)	24.7 (21.9–27.4)	15.5 (13.3–17.7)	41.7 (38.4–44.9)	22.5 (19.9–25.1)	28.1 (25.3–30.8)

Table 3. Logistic regression analysis of predictors of Chronic NCD risk factors clustering (≥ 3) (95% CI) in nine Asian HDSS sites

| | Bangladesh | | | | India | Vietnam | | Indonesia | Thailand |
	Matlab	Mirsarai	Abhoynagar	WATCH	Vadu	Chililab	Filabavi	Purworejo	Kanchanaburi
Sex									
Women	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Men	1.2 (0.98–1.5)	0.9 (0.8–1.2)	1.0 (0.8–1.3)	1.4 (1.1–2.0)	1.2 (0.9–1.5)	9.0 (5.7–14.2)	8.7 (6.6–11.3)	1.6 (1.3–2.0)	1.6 (1.3–1.9)
Age groups (years)									
25–34	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
35–44	1.4 (1.0–1.9)	1.5 (1.1–2.1)	1.7 (1.1–2.5)	1.1 (0.7–1.8)	1.8 (1.3–2.6)	1.2 (0.8–2.0)	1.3 (0.91–1.8)	1.5 (1.0–2.2)	1.29 (0.94–1.78)
45–54	1.9 (1.4–2.6)	2.2 (1.6–3.0)	1.7 (1.1–2.5)	2.0 (1.2–3.1)	2.5 (1.8–3.5)	1.7 (1.1–2.6)	1.5 (1.1–2.1)	1.9 (1.3–2.7)	1.9 (1.39–2.61)
55–64	2.3 (1.7–3.1)	3.4 (2.5–4.6)	3.1 (2.1–4.4)	2.8 (1.8–4.3)	3.9 (2.7–5.6)	1.5 (0.9–2.3)	2.6 (1.9–3.7)	3.4 (2.4–4.9)	2.45 (1.8–3.33)
Highest education levels									
No schooling and not graduated from primary school	0.5 (0.4–0.7)	0.6 (0.4–0.8)	0.8 (0.5–1.4)	0.4 (0.2–0.6)	0.5 (0.4–0.7)	1.5 (0.8–2.8)	1.0 (0.6–1.5)	0.5 (0.4–0.8)	1.13 (0.78–1.65)
Graduated from primary school	0.6 (0.4–0.9)	0.7 (0.4–1.1)	1.1 (0.6–2.1)	0.6 (0.3–1.0)	0.5 (0.3–0.7)	1.1 (0.7–1.8)	0.5 (0.3–0.8)	0.6 (0.4–0.8)	1.07 (0.75–1.53)
Graduated from secondary school	0.7 (0.4–1.1)	0.6 (0.4–1.0)	1.2 (0.7–2.2)	0.9 (0.5–1.6)	0.7 (0.5–1.0)	0.9 (0.7–1.3)	0.6 (0.5–0.9)	0.7 (0.5–1.1)	1.16 (0.72–1.88)
Graduated from high school or university	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

dbp ≥ 90 mmHg). Extensive clustering of risk factors (both biological and behavioural) was found to be a function of age, sex, and educational achievement. The implication of these findings for prevention and treatment is discussed.

The finding that the risk factors cluster as age advances is not surprising, as age-related biological risks (e.g. hypertension or obesity) are super-imposed upon the cumulative 'life-style' behavioural risk factors (e.g. tobacco and alcohol use, diet high in salt, fat and sugar and low in fruits and vegetables, physical inactivity, etc.) increase the probability of developing chronic NCDs (2). This is also consistent with the observation that the prevalence of chronic diseases increases with age (29–31).

Increasing level of educational achievements was associated with greater probability of risk factors clustering. This may be due to the fact that with increasing education also comes affluence (32, 33), and greater access to tobacco, alcohol, diets high in fats, salt, and sugar. However, education was also found to be associated with low probability of risk factors clustering in sites from Vietnam, possibly because higher level of education may also increase both awareness of, and capacity to take preventive actions against the common chronic NCDs (13). Modifying life-style factors through health promotion interventions, supported by policy such as tobacco control measures, may become more feasible as education improves.

However, perhaps the most useful aspect of looking at the constellation or clustering of major risk factors, is to identify the strata of individuals in a known population who may well be at high overall risk of a cardiovascular disease event. This high risk section of the population is the candidate for integrated management of multiple risk factors in a cost-effective way (34). In this study, the age group 55–64 years was found to be such a vulnerable group who had two to three times more probability of risk factors clustering compared to the younger age groups. This may also be the group who will benefit from recent preventive innovations such as the polypill (polycap) (35).

It is interesting to note the differences among the different sites with respect to prevalence of risk factors, both between and within country. This may be due to differences in the socio-cultural characteristics as well as economic development of the HDSS catchment populations (e.g. mobility and participation in public sphere, and concept of 'sports' and 'leisure' in case of women), representativeness of the sites (localised or geographical spread), timing of survey, and level of farm activities, etc. For example, gender differences at site level in Bangladesh and Vietnam can be explained by the characteristics of the HDSS catchment areas: the 10 data collection locations of WATCH HDSS is geographically spread all over Bangladesh while the Matlab and

AMK sites are localised to specific parts of the country. In case of Vietnam, Filabavi has 30 data collection locations compared to seven locations in Chililab; also, Chililab is mainly a peri-urban area compared to Filabavi which is predominantly rural. For more on this, please refer to other papers in this supplement. These variations among sites (and thereby countries) need to be kept in mind when designing preventive interventions.

The main strength of the study is the use of an established HDSS infrastructure which ensured a reliable sampling frame, mutual trust, and respect between the researchers and the respondents which has been built over time. Together with the use of standard protocols, it was also possible to link the data with other health and demographic data. These are discussed in more detail in the design paper (28).

A limitation of the HDSS sites is that they are not representative of their respective countries due to non-random, convenient placement of the study sites; however, they provide an indication of what is happening in these selected well-defined populations. Other limitations include: the socio-cultural context in the construction of the different risk factors, the possibility of measurement errors including measurement of prevalence based on self-reported responses, and the possibility of recall bias. Quality control efforts were made by following the STEPS methodology, training (for the principal investigators), use of common measuring instruments (digital BP machines, measuring tape, and weighing scale), and intensive monitoring and supervision of field activities. Some results were well outside the expected responses and raised the need for qualitative exploration for a fuller understanding of the quantitative data (e.g. why Asian populations consume little fruits and vegetables despite their availability, at least the indigenous varieties).

The findings suggest a need for the adoption of population-based approaches to prevention, and the need for information on which to base cost-effective interventions to reduce individual risk (36). This needs appropriate adjustment to the particular context of low-income countries (37). A life-cycle approach to preventive interventions such as reducing salt intake and controlling tobacco use at the population level (38) may forestall the cummulative effects of multiple risk factors which occur over time (39). At the individual level, interventions targeted at vulnerable groups such as older age groups with three or more risk factors may be helped by identifying the section of the population who could benefit from cost-effective interventions (40). Even so, our study suggests that further refinement (e.g. the elderly with sbp >160 mmHg) will be required to identify a smaller group of individuals who could benefit from individual intervention.

Conclusions

In conclusion, it can be said that since there is an extensive clustering of risk factors for the chronic NCDs in the populations studied, the interventions also need to be based on a comprehensive approach rather than on a single factor to forestall its cumulative effects which occur over time. That such integrated, life-style interventions work in the developing country settings is already documented (37). In low and middle-income countries, this can work best if it is integrated within the primary health care system for optimal benefit and convenience and the HDSS can be an invaluable epidemiological resource in this endeavor (41).

Conflict of interest

The authors have declared no conflict of interest.

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