Factors influencing tobacco use treatment patterns among Vietnamese health care providers working in community health centers

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Abstract
Background: Almost half of adult men in Viet Nam are current smokers, a smoking prevalence that is the second highest among South East Asian countries (SEAC). Although Viet Nam has a strong public health delivery system, according to the 2010 Global Adult Tobacco Survey, services to treat tobacco dependence are not readily available to smokers. The purpose of this study was to characterize current tobacco use treatment patterns among Vietnamese health care providers and factors influencing adherence to guideline recommended tobacco use screening and cessation interventions.

Methods: A cross sectional survey of 134 health care providers including physicians, nurses, midwives, physician assistants and pharmacists working in 23 community health centers in Viet Nam.

Results: 23% of providers reported screening patients for tobacco use, 33% offered advice to quit and less than 10% offered assistance to half or more of their patients in the past three months. Older age, attitudes, self-efficacy and normative beliefs were associated with screening for tobacco use. Normative beliefs were associated with offering advice to quit. However in the logistic regression analysis only normative beliefs remained significant for both screening and offering advice to quit. Over 90% of providers reported having never received training related to tobacco use treatment. Major barriers to treating tobacco use included lack of training, lack of referral resources and staff to support counseling, and lack of patient interest.

Conclusions: Despite ratifying the FCTC, Viet Nam has not made progress in implementing policies and systems to ensure that smokers are receiving evidence-based treatment. This study suggests a need to change organizational norms through changes in national policies, training and local system-level changes that facilitate treatment.

Keywords: Cessation, Tobacco, Clinical practice guidelines, Adherence guidelines, Viet Nam

Background
Almost half of adult men in Viet Nam are current smokers, a smoking prevalence that is the second highest among South East Asian countries [1]. Although smoking rates among women are low (1.4%), exposure to second-hand smoke is significant, ranging from 55.3-67.6% [1-3]. If current smoking rates are not addressed it is estimated that in 10 years, tobacco use will be responsible for about 25% of adult male deaths in Viet Nam [4].

Evidence-based, cost effective approaches to treating tobacco use exist and are defined by the U.S. Public Health Service Guideline (PHS Guideline) on Treating Tobacco use and Dependence [5]. The Guideline, which is endorsed by the World Health Organization (WHO), is based on a meta-analysis of over 6000 studies and provides strong evidence that asking all patients about tobacco use, advising smokers to quit, assessing readiness, providing assistance (e.g., counseling) and arranging follow-up (the 5As) can significantly increase smoking abstinence rates [5]. Yet, in the U.S. and globally, adoption of guideline recommended care into routine public health and clinical practice is suboptimal [6,7].
Implementing evidence-based tobacco use treatment is a core provision in the WHO Framework Convention on Tobacco Control (FCTC). The FCTC is an evidence-based treaty that was developed by the WHO in response to the globalization of the tobacco epidemic [8]. Article 14 of the WHO FCTC states “each country shall take effective measures to promote cessation and adequate treatment for tobacco dependence” [9]. In an effort to comply with Article 14, over 20 countries have developed guidelines for treating tobacco use [10]. Although Viet Nam has a strong public health delivery system, according to the 2010 Global Adult Tobacco Survey (GATS), services to treat tobacco dependence are not readily available to smokers [1]. The dearth of effective tobacco cessation services in Viet Nam is not the result of a lack of commitment to tobacco control. The government ratified the FCTC in 2004, and has enacted an ambitious National Tobacco Control Action Plan (Decision No. 1315/QD-TTg) for the Implementation of the FCTC.

Despite the high rates of tobacco use in Viet Nam we are not aware of any studies that have assessed smoking cessation practice patterns among Vietnamese health care providers. Moreover, we are not aware of any studies that have assessed perceived barriers to adhering to clinical practice guidelines or normative beliefs in relation to treating tobacco use among health care professionals in South East Asian Countries (SEACs). These factors have been shown to influence provider adherence to guideline recommended care across a range of preventive services [11-15]. Therefore, understanding the association between these potentially modifiable factors and tobacco use treatment practice patterns may help guide policy and system changes to address gaps in implementing comprehensive smoking cessation interventions throughout the public health system in Viet Nam and other SEACs.

Within this context, the aim of this paper is to characterize current cessation intervention practices and examine behavioral and organizational factors that may influence adherence to recommended guidelines for treating tobacco use among health care providers working in commune health centers in Hanoi, Vietnam [14,16].

Methods
Study overview

The study was conducted as part of a formative evaluation prior to implementing a randomized controlled trial study to assess strategies for implementing tobacco use treatment guidelines in the public health system in Viet Nam. The study was conducted in Dong Anh district - a suburban district in Hanoi, the capital city of Viet Nam. With approval from the director of District Health Center, 23 commune health centers were invited to participate. Subsequent staff meetings were held at each site to describe the study in more detail. Follow-up appointments were made with staff who agreed to participate. Participants received $4 (80,000 VND) each as compensation for their time. The institutional review boards of the Institute of Social Medical Studies (ISMS) and the New York University School of Medicine approved this research.

Study sites

The Vietnamese health care system is hierarchically organized into four administrative levels: central, province, district and commune. At the central level is the Ministry of Health (MOH), the main national authority in the health sector which formulates and implements national health policies and programs. The provincial-level health system consists of Provincial Health Departments and Preventive Health Centers, which are administered by the Provincial People’s Committee in each province. At the district level, the District People’s Committee administers district health centers and district-level hospitals. Within districts the commune health centers (CHCs) serve as the primary access point for public health and preventive care services in Viet Nam, each providing services for an average of 5000–7000 people in their surrounding community.

CHCs are charged with implementing 10 national health programs, diagnosis and treatment of common diseases, provision of health counseling and education, referral services, pre- and post-natal care, family planning, and food hygiene and safety. Each CHC is staffed by 5–6 health care providers, including one physician and three to five other health professionals (Physician assistants, nurses, midwives and/or pharmacists). In addition, each CHC is supported by a network of 8–10 village health workers (similar in roles and responsibilities to community health workers) who primarily conduct outreach work in the villages within a commune.

Study design and measures

In November 2012 a cross sectional survey was conducted with 134 health care providers including physicians, nurses, physician assistants, pharmacists and midwives practicing in 23 CHCs. After obtaining verbal consent, a trained research assistant from ISMS administered the surveys in person. The survey measured demographic data (e.g., gender, age), smoking status and current practice patterns related to tobacco use treatment. Current smoking was defined as having smoked at least 100 cigarettes in their lifetime and having smoked some days or everyday. Former smokers were defined as those who smoked >100 cigarettes during their lifetime but answered not at all in response to the question, do you now smoke every day, some days, or not at all? Provider adherence to guideline recommended tobacco use treatment was assessed using a validated tool that assessed four of the 5As with the following questions: In the past three months 1) How many new patients did you ask about their tobacco use status?
2) Among all of your patients, how many did you ask about their tobacco use status? 3) For how many patients who are tobacco users did you assess readiness to quit? 4) How many patients who are tobacco users did you give advice or counsel to quit, 5) How many patients who are tobacco users did you refer to a community stop smoking program or counselor for help quitting, and 6) How many patients who are tobacco users did you prescribe smoking cessation medication like the nicotine patch [17]. Using a 5-point likert scale answers included none, few, half, more than half or all or most.

They survey also examined factors that may influence provider adherence to tobacco use treatment guidelines. These questions were informed by the Theory of Planned Behavior (TPB) which posits that individual cognitions including attitudes towards a behavior and social norms related to performing a behavior guide individual actions [15]. In addition to being one of the most widely tested theories for predicting individual behavior change, TPB has been shown to be able to predict clinician behavior [11-15]. Questions measuring TPB constructs were adapted from Francis and colleagues and the WHO Global Health Professional Survey [11,18].

All of the questions used a 4-point likert scale (strongly disagree, disagree, agree, strongly agree). Attitudes were measured with four questions: 1) most smokers do not want to quit, 2) advice from a doctor or nurse in one of the best ways to help people stop smoking, 3) smoking cessation counseling is not a priority to me, and 4) patients appreciate it when I provide smoking cessation counseling. Normative beliefs were measured with two questions: 1) my supervisors think that helping smokers quit is a priority, and 2) most of the staff thinks that promoting smoking cessation is part of their job. Self-efficacy was measured with three questions: 1) I am confident in my ability to help patients stop smoking, 2) I have the training I need to help smokers quit smoking, and 3) I am not aware of the best treatments for helping patients stop smoking. Barriers were assessed using a 4-point likert scale ranging from not a barrier to major barrier. Questions about barriers were based on previous literature from studies in China and the US [16,19]. The surveys were translated from the English version to the Vietnamese version and then back-translated to English before conducting a pilot test with 10 participants to assess comprehension and relevance.

**Data analysis**

A data entry specialist entered the survey information into the database in EpilInfo V.6.04. To ensure accuracy, 10% random samples of the data were cross validated by the data entry specialist and research assistants. Data were analyzed by using IBM SPSS Statistics for Windows version 20.0 (Armonk, NY: IBM Corp.). Descriptive statistics were used to summarize the provider and site characteristics, responses to questions about barriers to treatment, attitudes, norms and self-efficacy as well as rates of asking, advising, assessing readiness to quit and offering cessation assistance. Scores on individual items were averaged within each TPB-related construct to produce a composite measure for analysis. We reversed negative questions about attitudes and self-efficacy so that a high summary score always indicated stronger or more positive beliefs.

We used Chi square analysis, T-test and logistic regression to assess the relationships between variables. Smoking status and gender were highly correlated; therefore we included only gender in the analyses. Significance was established as p ≤ 0.05 (2-tailed).

**Results**

Ninety five percent of providers working in the 23 CHCs completed the survey. Table 1 shows characteristics of the participating health professionals and the CHCs in which they work. Consistent with national data in Vietnam, 80% of the health care providers were female (10% physician, 73% nurse or Physician Assistant) [20]. Less than 10% were current smokers and these were all male clinicians. Ninety four percent had not participated in formal training on tobacco use treatment. Among the 74% who reported a smoking policy in their CHC, only 26.5% reported a total ban.

**Table 1 Provider and practice characteristics**

| Characteristic                  | N   | %/Mean (SD) |
|--------------------------------|-----|-------------|
| **Gender**                     |     |             |
| Male                           | 27  | 20.1%       |
| Female                         | 107 | 79.9%       |
| **Age (mean years)**           |     | 37.4 (10.0) |
| **Profession**                 |     |             |
| Physician                      | 14  | 10.4%       |
| Nurse                          | 50  | 37.3%       |
| Midwife                        | 18  | 13.4%       |
| Physician’s assistant          | 49  | 36.6%       |
| Pharmacist                     | 3   | 2.2%        |
| **Smoking status**             |     |             |
| Current                        | 13  | 9.7%        |
| Never                          | 109 | 81.3%       |
| Former                         | 12  | 8.9%        |
| **Have NOT participated in tobacco use treatment training** |   |             |
| No                             | 17  | 12.7%       |
| Yes                            | 98  | 73.1%       |
| Don’t know                     | 19  | 14.2%       |
Over 90% agreed or strongly agreed that advice from a provider is one of the best ways to help people stop smoking, but almost half reported that offering smoking cessation counseling is not a priority for them (Table 2). Self-reported levels of confidence were in conflict with reports of training and awareness of best treatment. Over 85% reported that they were confident in their ability to help smokers, but 60% agreed or strongly agreed that they were not aware of the best treatment to help patients stop smoking and only 29% agreed or strongly agreed that they had the training needed to help smokers quit. Over 80% agreed or strongly agreed that offering smoking cessation treatment was part of their job and that their supervisor thinks that helping smokers is a priority. Table 2 also shows the percent of providers who reported adherence to guidelines for screening and treating tobacco use. Twenty-three percent of providers reported screening half or more of their patients, 33% provided advice to smokers, and less than 10% offered assistance (i.e., counseling, referral or medication) to half or more of their patients.

The most commonly reported barriers to treatment (Figure 1) were lack of training (70%) lack of referral resource in the community or additional staff to assist with cessation counseling (69%) and lack of patient interest (80%). Table 3 shows the results of the bivariate analysis examining the correlation between provider practice patterns and provider characteristics, smoke free policies and TPB constructs. Older age, self-efficacy, attitudes and norms that endorsed tobacco use treatment were associated with providers routinely screening half or more of their patients. Routinely offering advice to quit was associated with normative beliefs.

In the multiple logistic regression analyses (Table 4) normative beliefs was the only factor that remained significantly associated with asking about tobacco use (OR 3.47, p < .014) and advising patients to quit (OR 5.15, p < .005).

### Discussion

Vietnamese providers working in CHCs in Hanoi reported low rates of tobacco use screening (23%). Although once smokers were identified providers were more likely to advise smokers to quit (33%), less than 10% provided more in-depth cessation assistance (i.e., brief counseling, referral or prescription). Similarly, a survey among 447 physicians in Indonesia found low rates of adherence to recommended screening and cessation treatment practices (e.g., 28% routinely asked about patients’ smoking status) [21]. In contrast, surveys of hospital-based physicians in China have found higher rates tobacco use screening and advise to quit. In a study in five hospitals in China 71% of physicians reported asking about smoking and 78% offering advice to quit [22]. A 2004 survey of 3552 hospital-based

### Table 2 Attitudes, self-efficacy, norms and practice patterns related to treating tobacco use

| Constructs                                      | N (%) Agree/Strongly agree | Mean (SD) |
|-------------------------------------------------|----------------------------|-----------|
| **Attitudes**                                   |                            |           |
| Offering smoking cessation treatment to my patients is part of my job. | 116 (86.6) | 3.30 (0.78) |
| Most smokers don’t want to quit.                | 94 (70.1) | 2.98 (0.99) |
| Smoking cessation counseling is not a priority to me. | 71 (53.0) | 2.40 (0.96) |
| Advice from a doctor or nurse is one of the best ways to help people stop smoking. | 129 (96.3) | 3.75 (0.54) |
| Patients appreciate it when I provide smoking cessation counseling. | 111 (82.8) | 3.2 (0.77) |
| **Self-efficacy**                               |                            |           |
| I am confident in my ability to help patients stop smoking. | 117 (87.3) | 3.22 (0.78) |
| I have the training I need to help smokers quit. | 39 (29.1) | 1.93 (1.06) |
| I am not aware of the best treatments for helping patients stop smoking. | 80 (60.2) | 2.64 (1.03) |
| **Norms**                                       |                            |           |
| Most of the staff think that promoting smoking cessation is part of their job | 120 (89.6) | 3.40 (0.73) |
| My supervisors think that helping smokers quit is a priority. | 112 (83.6) | 3.23 (0.76) |
| **Practice patterns (in past 3 months)**       | Half or more patients      |           |
| Ask about tobacco use                           | 31 (23.1) |           |
| Advise to quit                                  | 32 (33.0) |           |
| Assess readiness to quit                        | 14 (14.4) |           |
| Assist**                                        | 8 (8.3) |           |

*aCronbach’s alpha = 0.32, bCronbach’s alpha = 0.27, cCronbach’s alpha = 0.42.

4 point likert scale included: none, few, half, more than half or all or most.

**Assisted is defined as referring patients for counseling and/or prescribing cessation pharmacotherapy.
physicians from six Chinese cities found that 48% screened for tobacco use and 64% reported advising smokers to quit however, only 7% offered pharmacotherapy [23].

Lower rates of adherence to guideline recommendations in this study may be due to the focus on community-based clinicians and inclusion of non-physician health care professionals. Over 90% of providers in this study reported no previous training related to tobacco use treatment and less than a third reported they had the training needed to help smokers quit. Ng and colleagues found that community physicians in Indonesia were less likely to screen for tobacco use or offer advice to quit compared with medical school faculty and residents. They were also less likely to feel that they had sufficient training or experience to help smokers quit [21]. Not having an affiliation with an academic institution or major hospital may diminish opportunities for training on tobacco use treatment among clinicians in CHCs, particularly if this is not considered a national prevention priority for CHCs to manage, as is the case in Viet Nam.

We are aware of only two other studies that have included community-based health care professionals in assessments of tobacco use treatment [21,23]. Yet, CHCs are the front line for preventive service delivery in Viet Nam and other low-middle income countries (LMICs). A program that offers training of physicians and allied health professionals working in CHCs is urgently needed. Global Bridges, a not for profit organization, is providing evidence-based training in treatment and advocacy and is working towards implementing Article 14 in four regions but has not yet expanded this program to include SEACs [24]. Additional funding should be directed toward building capacity among provider organizations and Ministries of Health to disseminate tobacco use treatment-related education and training programs throughout public health care delivery systems in these countries.

Table 3 Correlates of tobacco use screening and advise to quit delivered by health care providers

| Constructs                | Asked | p-value | Advised to quit |
|---------------------------|-------|---------|-----------------|
|                           | None or few patients | Half or more | None or few patients | Half or more | p-value |
| Age                       | 36.2 (9.71) | 41.48 (10.17) | .01 | 36.4 (10.06) | 39.66 (9.90) | .13 |
| Gender                    | .20    |         |                 | .09 |
| Female                    | 85 (79.4%) | 22 (20.6%) | .01 | 52 (72.2%) | 20 (27.8%) | .52 |
| Male                      | 18 (66.7%) | 9 (33.3%) | 13 (52.0%) | 12 (48.0%) |
| Smoking status            | 1.0    | .52     |                 | 1.0 |
| Current smoker            | 10 (76.9%) | 3 (23.1%) | 7 (58.3%) | 5 (41.7%) |
| Former or nonsmoker       | 93 (76.9%) | 28 (23.1%) | 58 (68.2%) | 27 (31.8%) |
| Clinic smoking policy     | 1.0    | .01     |                 | 1.0 |
| Yes                       | 74 (75.5%) | 24 (24.5%) | 49 (66.2%) | 25 (33.8%) |
| No                        | 13 (76.5%) | 4 (23.5%) | 10 (71.4%) | 4 (28.6%) |
| Mean score attitudes      | 2.9 (0.43) | 3.1 (0.39) | .01 | 3.0 (0.40) | 3.1 (0.40) | .41 |
| Mean score self-efficacy  | 2.4 (0.64) | 2.7 (0.53) | .02 | 2.5 (0.60) | 2.6 (0.45) | .27 |
| Mean score norms          | 3.2 (0.61) | 3.6 (0.42) | <.001 | 3.3 (0.52) | 3.6 (0.54) | .01 |

Means with SD in parenthesis are show for continuous variables; counts with percentages are shown for categorical variables. T-test was used for continuous variables and Chi square test for categorical variables.
Vietnamese health care provider’s attitudes towards delivering cessation interventions were generally positive. Similar to previous surveys of providers practicing in China and other SEACs, the discrepancy between attitudes and practice may be largely related to a lack of knowledge about treatment strategies. Several studies have found a significant association between lack of training and low cessation intervention activities among physicians [21-23,25]. Although our smaller sample size and the lack of heterogeneity in this response (94% reported no training) may have precluded our ability to demonstrate this association, a lack of training was one of the top two barriers, cited by providers, to adhering to tobacco use treatment guidelines.

Another finding that may be related to a lack of training was the large percentage of providers that agreed with the statement that smokers don’t want to quit (70%). A lack of patient interest in quitting was also the most frequently cited barrier to asking about tobacco use and offering cessation assistance. This belief is not supported by national data and may have contributed to the low rates of tobacco use screening. According to the 2010 Global Adult Tobacco Survey, two-thirds of current smokers in Vietnam are planning to or thinking about quitting and over half attempt to quit annually [26]. Other reported barriers suggest that gaps in staffing and systems to facilitate routine screening and treatment, are also contributing to low levels of cessation interventions. A study of hospital-based physicians in China found that organizational support was associated with a greater level of physician delivered advice to quit [26]. Although not well studied in LMICs, there is a large literature supporting the need for organizational and system level changes to enhance adoption of the full spectrum (5As) of evidence based tobacco use treatment [5,6,27].

Similar research is needed to test strategies for implementing and dissemination guidelines in these critically important preventive health care delivery settings. Novel models of care that address the lack of staff and referral resources could include leveraging the robust community health worker infrastructure in many LMICs, including Viet Nam, to serve as a referral resource in the same way that smoker telephone quitlines offer providers in several countries an evidence-based counseling option for their patients [6,28-31].

Further examination of variables specified by the TPB showed that only normative beliefs, which have not been evaluated in previous surveys of providers in LMICs, were strongly associated with tobacco use screening and cessation advice. A study in China did find that providers with positive attitudes towards treatment were significantly more likely to ask about tobacco use but similarly found no association with cessation advice [26]. This is in contrast to two recent systematic reviews suggest that TPB and the lack of heterogeneity in this response (94% reported no training) may have precluded our ability to demonstrate this association, a lack of training was one of the top two barriers, cited by providers, to adhering to tobacco use treatment guidelines.

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Table 4 Multiple logistic regression

| Independent variables | Asked (n = 115) none or few vs. half or more | Advised to quit (n = 88) none or few vs. half or more |
|-----------------------|---------------------------------------------|------------------------------------------------------|
|                       | OR (95% CI) p-value                          | OR (95% CI) p-value                                  |
| Age                   | 1.06 (1.01-1.12) .020                        | 1.05 (0.99-1.11) 0.10                                 |
| Female                | 1.04 (0.34-3.16) .952                        | 0.51 (0.16-1.61) 0.25                                 |
| Smoking policy        | 0.91 (0.23-3.59) .894                        | 1.15 (0.29-4.65) 0.843                               |
| Attitudes             | 1.75 (0.45-6.83) .418                        | 0.59 (0.15-2.41) 0.463                               |
| Self-efficacy         | 1.39 (0.57-3.37) .471                        | 0.81 (0.29-2.26) 0.69                                 |
| Norms                 | 3.47 (1.28-9.38) .014                        | 5.15 (1.65-16.1) 0.005                               |

Among the top two barriers, cited by providers, to adhering to tobacco use treatment guidelines.

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Our finding of a strong association between norms and tobacco use screening and advice to quit may be related to Viet Nam’s cultural emphasis on collectivism and CHC’s focus on implementing only those practices that are consistent with national and provincial priorities. This finding, albeit drawn from one district in Hanoi, emphasizes the need to work with and obtain support from organizational authorities (i.e., Ministry of Health and District Health leaders) for implementing and disseminating tobacco use treatment guidelines into routine preventive services in CHCs. A recent analysis of experience building capacity for implementation of the FCTC for tobacco control in Viet Nam found that organizational infrastructure, leadership and expertise, partnership and networks and data and evidence from research were key components in efforts to meet FCTC commitments, including the goals of Article 14 [32].

Clearly a wide range of factors can influence clinical practice including individual beliefs as well as political and organizational context [16,33]. However, our understanding of these factors is incomplete, particularly in LMICs. Future research should incorporate both individual and organizational level theories to better inform the design of interventions to increase guideline-concordant tobacco use treatment.
Similar to previous surveys of health care providers in SEACs we found that smoking rates among health care providers were significantly lower than national average [1,18]. In this, and the only other survey of Vietnamese providers, the low smoking rates are explained by low rates of smoking among women who are disproportionately represented in the health care profession in Viet Nam [18]. Health care providers who do not smoke are more likely to express positive attitudes towards their role in offering cessation assistance to smokers, act as role models and influence social values, and are more likely to offer cessation services compared with providers who smoke [17,18]. Therefore, the consistent finding that prevalence is low among health care providers practicing in CHCs in Viet Nam offers additional incentive to focus efforts on training and system changes in these settings.

Limitations of the study include the small sample size and surveying providers in a suburban setting only. Clinicians working in more rural areas may have different perspectives and practice patterns. We also did not include community health workers in the survey. We are not aware of other tobacco-related provider surveys that have included this workforce. However, there is tremendous untapped potential for CHWs to contribute to a team approach to enhancing screening and treatment for tobacco use.

Conclusion
CHC’s focus on preventive care, their role as the first access point for the health care system and the availability of services at no cost to a large majority of the population makes them the ideal setting for implementing routine tobacco use screening and treatment. However, closing the gap between evidence for tobacco use treatment and current practices in CHCs in Viet Nam will require changes in national preventive health services priorities to specifically include Article 14 goals and policies that support implementation of these goals. These include requirements for evidence-based training of all health care professionals, including community health workers, redefining the role of the care team members to identify those responsible for screening and treatment and creating referral options that support provider cessation interventions. Having ratified the FCTC, created an office in the MOH for tobacco control and passed into law a plan to implement a comprehensive tobacco control program Viet Nam is poised to develop replicable models of care delivery that address gaps in the reach and sustainability of evidence-based tobacco use treatment that could lead to significant reductions in tobacco related morbidity and mortality.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
DS and NN conceived the study, developed the study protocol and the survey tool and wrote the manuscript. SK assisted with survey development and oversight of the study locally in Viet Nam. LN conducted the data collection and data entry. TT and HP conducted data analysis and edited the manuscript and FS assisted with survey design and review of the final manuscript. All authors read and approved the final manuscript.

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Received: 3 July 2013 Accepted: 13 December 2013
Published: 22 January 2014

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