tion showed that fewer than half of the respondents (210/503) had given antibiotics to the index child without a prescription for symptoms of upper respiratory tract infection such as cough (84%), fever (66%) or nasal (65%) and throat symptoms (60%). The main source of non-prescribed antibiotics was pharmacies (86%). Amoxicillin was the most commonly used non-prescribed antibiotic (58%), followed by ampicillin (25%), erythromycin (6%), chloramphenicol (5%) and trimethoprim–sulfamethoxazole (5%). Most children took non-prescribed antibiotics for a period of 3 to 5 days (76%). Additionally, 8% of the children were treated with two non-prescribed antibiotics simultaneously, and 5% were given parenteral antibiotics if they had a sore throat with fever and cough or shortness of breath. Of the non-prescribed antibiotics, 31% were given on the advice of pharmacists, 35% on the advice of family members and 8% on the advice of friends. Reasons for not seeking a physician's advice included the belief that the illness was not severe (70%) and previous experience with the doctor always prescribing the same antibiotics for similar conditions (15%). Past experiences and familiarity with a drug were the main reasons for selecting a particular antibiotic (82%).

Table 1. **Characteristics of sample of caregivers (n = 503) and children included in survey on the non-prescribed use of antibiotics for children in Ulaanbaatar, Mongolia, 2009**

Characteristic	Value
Caretaker	
Relationship to child, no. (%)	
Mother	356 (71)
Father	66 (13)
Grandparent	81 (16)
Mean age, years (SD)	35.4 (11.9)
Education, no. (%)	
General[a]	183 (36.4)
College[b]	50 (9.9)
Institute or university[c]	270 (53.7)
No. of people in the household, mean (SD)	4.3 (1.1)
Religion, no. (%)	
Buddhist	370 (73.6)
None	114 (22.7)
Other	19 (3.4)
Ethnicity, no. (%)	
Khalkh	450 (89.5)
Other	23 (11.5)
Child	
Mean age, in months (SD)	28.3 (15.7)
Male, no. (%)	264 (52.5)

SD, standard deviation.
[a] General education: 10 years of basic education from ages 8 to 18 years.
[b] College education (vocational training): an additional 2 years of education following basic education (i.e. up to 12 years of education in total).
[c] Institute or university education: an additional 4 years of education following basic education (i.e. up to 14 years of education in total).

Knowledge about antibiotic use

Table 2 shows participants' knowledge of the appropriate use of antibiotics based on response alternatives from the Centers for Disease Control and Prevention (Atlanta, United States) as adapted by Huang et al.[10] The median number of questions that were correctly answered was four (range: 0–10). Many respondents gave incorrect answers about antibiotic use for colds or flu (83%), a cough (81%), sore throat (74%) or purulent nasal discharge (64%). There was also a lack of understanding of antibiotic use for clear nasal discharge (runny nose) and middle ear fluid: about half the respondents answered incorrectly. Most participants (96%) incorrectly believed that most colds and cases of flu were caused by bacteria, and 76% incorrectly believed that antibiotics would accelerate recovery from these illnesses. A tendency to demand antibiotics was noted in 27% of participants.

Multivariate logistic regression

The odds ratios (ORs) for factors associated with the non-prescription use of antibiotics by the mother are shown in Table 3. Non-prescription use was positively associated with keeping antibiotics at home (95% CI: 1.04–2.79) and self-medication with antibiotics (95% CI: 3.8–10.5). Mothers with a higher score for knowledge of antibiotics were less likely to give their children antibiotics without a prescription (95% CI: 0.6–0.8), whereas respondents answering affirmatively to two or more items that investigated antibiotic demand were more likely to use non-prescribed antibiotics (95% CI: 1.4–4.0). The likelihood of treating a child with non-prescribed antibiotics increased with children's age (95% CI; 1.01–1.04).

Discussion

This study is the first community-based survey of non-prescription use of antibiotics in Mongolia. In both developed and developing countries, self-medication with antibiotics is common for illnesses presumed to be caused by a virus.[11,13,31,32] Although this practice is well known, few previous studies have used research methods that allow their findings to be compared with those from earlier studies. However, the methods used in the present study make it possible to document that the prevalence of non-prescription use of antibiotics for children in Ulaanbaatar, Mongolia is higher (42%) than in earlier reports from rural communities in Viet Nam (12%) based on a 2-week recall period,[13] and from a Chinese city (35.7%) where the recall period was 12 months.[11]

Acute respiratory infection was the condition associated most frequently with non-prescription antibiotic use, a result which substantiates findings from other Asian countries.[11,13] Our results are also consistent with findings in China, where low-severity illness was a major reason for giving children antibiotics.[11] Most of our respondents used antibiotics because they considered themselves to be knowledgeable about antibiotic use, based on their past experience. This reason runs counter to findings from other developing countries, where relatively lower costs have been given as the main reason for self-medication.[33,34] The difference in motives may be related to good health insurance coverage in Mongolia, especially

Table 2. **Knowledge regarding appropriate antibiotic use and tendency to demand antibiotics among caregivers (n=503) in Ulaanbaatar, Mongolia, 2009**

Item	Response	No.	%
Questionnaire item	**Acceptable response[a]**		
How often are antibiotics needed for the following?			
Middle ear fluid without fever	Never/almost never	217	54
Clear nasal discharge (runny nose)	Never/almost never	237	47
Purulent nasal discharge	Never/almost never	179	36
Sore throat	Sometimes/almost never	130	26
Colds or flu	Never/almost never	84	17
Cough	Never/almost never	94	19
Ear infections	Sometimes/almost always	315	63
Are antibiotics helpful for treating bacterial infections, viral infections, or both?	Bacterial	100	20
Do most cold, cough and flu illnesses get better faster with antibiotics?	Disagree or strongly disagree	120	24
Are most cough, cold and flu illnesses caused by bacteria or viruses?	Viruses	22	4
Demand-related items	**Affirmative response[a]**		
If I expected an antibiotic, I am less satisfied with a doctor's visit if I do not receive an antibiotic.	Strongly agree or agree	150	30
I would rather give my child an antibiotic that may not be needed than wait to see if s/he gets better without it.	Strongly agree or agree	184	37
If a doctor does not prescribe an antibiotic when I think one is needed, I will take my child to another doctor.	Strongly agree or agree	137	27

[a] Acceptable and affirmative responses were adapted from reference Huang SS et al.[10]

in urban areas, where health services are free for children.[35,36]

Although the non-prescription sale of antibiotics is illegal in Mongolia,[18] our results replicate findings from other studies in settings where pharmacies were the main source of antibiotics for self-medication.[11,32,37] In contrast, countries where over-the-counter antibiotics sales are strictly regulated have much lower prevalence rates of self-medication with antibiotics, ranging from 1% to 4%.[31] The widespread availability of antibiotics without a prescription has given rise to concerns about their increased usage.[38] The uncontrolled use of antibiotics can be harmful because of adverse drug reactions, masking of symptoms of infection, the development of chronic disease and superinfection. It is also associated with the emergence and spread of antimicrobial resistance.[39] These problems require appropriate measures by policy-makers to develop pertinent policies as well as to ensure their implementation.

Keeping antibiotics at home was another important factor linked to the non-prescription use of antibiotics for children.[40] Leftover antibiotics may be available because of over-prescription or patient non-compliance with a course of treatment. It is therefore essential for physicians to appropriately prescribe the correct dosage, properly instruct patients to complete antibiotic courses, and encourage them to discard any leftover drugs.[7]

We found that 49.7% (250/503) of the children in households that participated in this study used prescribed antibiotics, and 50.2% (107/213) of the children who were given antibiotics by their caregiver used both prescribed and non-prescribed antibiotics. This practice can be traced back to Soviet-influenced health care practices, which included the prescription of heavy medication and injection usage.[41] Effective strategies to reduce the use of antibiotics include the development of policies to support the judicious use of antibiotics, strengthen the control of antibiotics consumption in clinical practice, and implement educational campaigns for prescribers.[42,43]

In line with another study,[11] we found that higher age of the index child was linked to a greater likelihood of parental non-prescription use. When younger children become ill, parents may

Table 3. **Odds ratios for risk factors linked to the use of non-prescribed antibiotics for children among mothers (n=465)[a] included in survey in Ulaanbaatar, Mongolia, 2009**

Independent variables	Value	95% CI	OR	95% CI
Distance to family medical facility (%)				
≤10 minutes	55.3	50.6–60.1	1.0	–
11–20 minutes	25.5	21.6–29.9	1.1	0.6–2.0
>20 minutes	19.1	15.6–23.2	1.6	0.8–3.1
Keeping antibiotics at home (mean no.)	58.4	53.6–63.0	1.7	1.04–2.79
Mean age of mothers (years)	30.3	29.8–30.8	1.0	0.9–1.07
Mother's education >10 years (%)	69.0	64.4–73.3	1.2	0.7–2.2
Mother having self-medicated with antibiotics (%)	34.8	30.4–39.5	6.3	3.8–10.5
Tendency to demand antibiotics (%)	27.0	23.0–31.5	2.4	1.4–4.0
Knowledge about URTIs and of antibiotics (mean score out of 10)	3.5	3.3–3.7	0.7	0.6–0.8
Wealth index score[b]	–0.01	–0.10–0.08	0.9	0.7–1.2
Mean age of index child (months)	28.7	27.2–30.3	1.02	1.01–1.04

CI, confidence interval; OR, odds ratio; URTI, upper respiratory tract infection.

[a] For the logistic regression analysis, only responses from households in which the primary caregiver was the child's mother were included.

[b] Calculated as described in Rutstein SO & Johnson K.[28]

be more careful and concerned and more likely to visit a doctor, whereas when the children are older, parents may have more knowledge about common illnesses and be more inclined to administer medical treatments themselves.

In countries that restrict over-the-counter antibiotics sales, studies of antibiotic use and parental knowledge have shown that patient's expectations about antibiotics influence their prescribing behaviour.[3,9,10,44] These findings mirror those in our study: parents' past experience, expectations and knowledge level appeared to influence non-prescription medication practices. In particular, caregivers who had medicated themselves with antibiotics were more likely to give antibiotics to their children without a prescription.

Caregivers also had misconceptions about self-medication. Most respondents in our study believed that antibiotics were needed for colds or flu, purulent nasal discharge and cough, even though these are typical manifestations of upper tract respiratory infections, most of which are caused by viruses. Past exposure was also an influence: if antibiotics were previously prescribed for an infection and the child later developed similar symptoms, than a caregiver was more likely to use antibiotics.[44] Educational interventions for caregivers regarding acute respiratory tract infections and antibiotic use can reduce the inappropriate use of antibiotics. Previous interventions have included the distribution of educational materials to hospitals and pharmacies, and the communication of information through the media.[9,42,45]

The use of non-prescribed medications for children might be a consequence of poor oversight of community pharmacies, and the widespread availability of medicines has probably contributed to an increase in this phenomenon. Interventions in other developing countries that have reduced over-the-counter antibiotic sales suggest, however, that this situation can be changed. In Chile, the prohibition of over-the-counter sales of antibiotics and a simultaneous public education campaign had an immediate and significant impact on the acquisition of antibiotics from pharmacies.[3] Similarly, sales of antibiotics without prescription in Zimbabwe decreased when the law against over-the-counter sales was strictly enforced. Fear of losing their license was a factor mentioned by some pharmacists for their compliance.[46]

This study has several limitations. Caregivers' self-reports about non-prescription use may be subject to recall bias. To minimize this possibility we limited the recall period to the previous 6 months, and attached a list of the most commonly used antibiotics to the questionnaires. We also asked participants to show us the antibiotics they kept at home. Another limitation is that findings from this urban sample cannot be generalized to the whole population of Mongolia. This would overestimate the prevalence of non-prescription antibiotic use since this study was done in the capital city, where access to pharmacies and information are higher than in rural settings. To better study this issue, future research should focus on both urban and rural areas, and should involve both prescribers and pharmacists. Additionally, seasonal variations in illnesses should also be taken into consideration, because they may have affected disease patterns and antibiotic use. As shown in a multi-country study in Europe, the attitudes and behaviour of health personnel may also reinforce self-medication with antibiotics,[14] although these factors were not examined in the current study. In the future, questions relating to the prescription of antibiotics, the doctor–patient relationship, patient satisfaction and perceived accessibility of health care should be included in survey instruments. The information obtained with these items will result in a better understanding of the determinants of non-prescription antibiotic use in Mongolia. Despite these limitations, our findings shed light on the relative importance of demand-side determinants related with non-prescription antibiotic use for children and the interventions needed to prevent this misuse.

Conclusion

The present study suggests that caregivers in Ulaanbaatar commonly use non-prescribed antibiotics for children younger than 5 years of age. Some determinants of this practice were the child's age, caregivers' misconceptions about the efficacy of antibiotics for upper respiratory tract infections, caregivers' own experience with self-medication, and the availability of antibiotics at home. Interventions aimed at preventing the unsanctioned use of antibiotics should be directed primarily at reducing the availability of non-prescribed antibiotics and educating the general public to dispel misconceptions about the use of antibiotics. ■

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ملخص

مسح عن استخدام أدوية الأطفال بدون وصفات طبية في مجتمع حضري في منغوليا

الغرض تقدير الانتشار والتعرف على محددات استخدام أدوية الأطفال بدون وصفات طبية في منغوليا.

الطريقة أُجْرِيَ مسح المقطع العرضي المرتكز على المجتمع في عشر مناطق فرعية في مدنية آولان باتار، عاصمة منغوليا. واستخدم الباحثون استبياناً لجمع المعطيات من عينة عشوائية مكونة من 540 أسرة لدى كل منها طفل واحد على الأقل دون عمر خمس سنوات. وأجري اختبار التحوف اللوجستي لتحديد العوامل المرتبطة بسوء استخدام المضادات الحيوية.

الموجودات من بين 503 من مقدمي الرعاية المشاركين في الدراسة، كوّنت الأمهات 71% منهم؛ استخدم 42.3% من مقدمي الرعاية (فاصلة الثقة 95%: 37.8 – 46.9) مضادات حيوية بدون وصفات طبية لمعالجة الأعراض التي ظهرت على أطفالهم خلال الشهور الستة السابقة. واشتملت الأعراض الشائعة التي عولجت على السعال (84%)، والحمى (66%)، ورشح الأنف (65%)، والتهاب الحلق (60%). وكان أموكسيسيلين هو أكثر المضادات الحيوية استخداماً (58%). وكانت الصيدليات هي المصدر الرئيسي لصرف الأدوية بدون وصفات (86%). وارتبط استخدام الأمهات للدواء بدون وصفات بالإبقاء على المضادات الحيوية في المنزل (نسبة الأرجحية: 1.7؛ وفاصلة الثقة 95%: 1.04 – 2.79)، والمعالجة الذاتية لمقدمي الرعاية (نسبة الأرجحية: 6.3؛ فاصلة الثقة 95%: 3.8 – 10.5)، وكبر عمر الطفل (نسبة الأرجحية: 1.02؛ فاصلة الثقة 95%: 1.01 – 1.04). أما مقدمو الرعاية الذين لديهم معرفة أفضل عن المضادات الحيوية فكان من الأرجح عدم إعطائهم

الأطفال مضادات حيوية بدون وصفات طبية (نسبة الأرجحية: 0.7؛ فاصلة الثقة 95%: 0.6 – 0.8).

الاستنتاج كان معدل انتشار استخدام المضادات الحيوية لصغار الأطفال بدون وصفات طبية عالياً في آولان باتار. ونظراً لأن هذا يؤدي إلى اتساع نطاق مقاومة البكتريا للمضادات الحيوية والمشاكل الصحية ذات الصلة، فإن نتائج هذه الدراسة لها آثار مهمة لتوعية العامة وتعزيز نظم بيع المضادات الحيوية في منغوليا.

Resumé

Enquête sur l'utilisation d'antibiotiques non prescrits chez les enfants d'une communauté urbaine de Mongolie

Objectif Estimer la prévalence et identifier les déterminants de l'utilisation sans prescription d'antibiotiques chez les enfants en Mongolie.

Méthodes Une étude communautaire transversale a été menée dans 10 sous-districts d'Oulan Bator, la capitale de la Mongolie. Nous avons utilisé un questionnaire structuré pour collecter des données à partir d'un échantillon aléatoire de 540 ménages comptant au moins un enfant âgé de moins de 5 ans. La régression logistique a été utilisée pour identifier les facteurs associés à l'usage abusif d'antibiotiques.

Résultats Sur 503 adultes référents ayant pris part à cette enquête, 71% étaient des mères; 42,3% (intervalle de confiance de 95%, IC: 37,8–46,9) des soignants avaient utilisé des antibiotiques non prescrits pour traiter les symptômes de leur enfant au cours des 6 mois précédents. Les symptômes fréquemment soignés étaient la toux (84%), la fièvre (66%), l'écoulement nasal (65%) et le mal de gorge (60%). L'amoxicilline était l'antibiotique le plus communément utilisé (58%). Les pharmacies étaient la principale source (86%) d'approvisionnement des antibiotiques non prescrits. L'administration d'antibiotiques sans ordonnance par les mères de famille était largement associée au fait que ces médicaments étaient conservés à domicile (rapport des cotes, RC: 1,7; IC de 95%: 1,04–2,79), à l'automédication par les soignants (RC: 6,3; IC de 95%: 3,8–10,5) et à l'âge plus élevé de l'enfant (RC: 1,02; IC de 95%: 1,01–1,04). Les adultes référents avec une meilleure connaissance des antibiotiques avaient moins tendance à administrer des antibiotiques non prescrits à leurs enfants (CR: 0,7; IC de 95%: 0,6–0,8).

Conclusion La prévalence de l'utilisation d'antibiotiques non prescrits chez les jeunes enfants était élevée à Oulan Bator. Cet usage abusif entraînant une augmentation de la résistance bactérienne aux antibiotiques, ainsi que des problèmes de santé connexes, nos résultats ont des implications importantes pour l'information du grand public et l'application de réglementations en matière de vente des antibiotiques en Mongolie.

Resumen

Estudio sobre el uso de antibióticos de venta sin receta en los niños en una comunidad urbana de Mongolia

Objetivo Calcular la prevalencia e identificar los factores determinantes para la prescripción de antibióticos de venta sin receta para niños en Mongolia.

Métodos Se realizó un estudio transversal de la comunidad en 10 subdistritos de Ulaanbaatar, la capital de Mongolia. Un cuestionario estructurado nos permitió recopilar los datos de una muestra aleatoria de 540 hogares, con al menos un niño menor de 5 años. Para identificar los factores asociados a la mala utilización de los antibióticos se empleó la regresión logística.

Resultados De los 503 cuidadores participantes, el 71% eran madres; el 42,3% (intervalo de confianza del 95%, IC: 37,8-46,9) de los cuidadores había utilizado antibióticos sin receta en los últimos 6 meses para tratar los síntomas de sus hijos. Los síntomas tratados más habituales fueron: tos (84%), fiebre (66%), mucosidad nasal (65%) y dolor de garganta (60%). El antibiótico más utilizado (58%) fue la amoxicilina. Los antibióticos de venta sin receta se obtuvieron principalmente (86%) en las farmacias. El uso de fármacos de venta sin receta por parte de las madres se asoció de manera significativa a la permanencia de los antibióticos en el hogar (oportunidad relativa, OR: 1,7; CI del 95%: 1,04-2,79), la automedicación de los cuidadores (OR: 6,3; CI del 95%: 3,8-10,5) y a la edad del hijo mayor (OR: 1,02; CI del 95%: 1,01-1,04). Los cuidadores que poseían conocimientos más amplios sobre los antibióticos fueron menos proclives a administrar antibióticos sin receta a los niños (OR: 0,7; CI del 95%: 0,6-0,8).

Conclusión La prevalencia del uso de antibióticos sin prescripción médica en los niños más pequeños fue elevada en Ulaanbaatar. Puesto que dicho uso conlleva un aumento de la resistencia bacteriana a los antibióticos y problemas relacionados con la salud, nuestros resultados tienen implicaciones importantes para la educación pública y para la aplicación de las normativas sobre la venta de antibióticos en Mongolia.

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添付資料 3

Global Health Metrics and Evaluation - a call for abstracts

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We declare that we have no conflicts of interest.

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Global Health Metrics and Evaluation—a call for abstracts

The Institute for Health Metrics and Evaluation (Seattle, WA, USA), *The Lancet*, the London School of Hygiene & Tropical Medicine, the Harvard School of Public Health, and the University of Queensland School of Population Health invite submission of abstracts for oral or poster presentation at their conference called Global Health Metrics and Evaluation: Controversies, Innovation, Accountability, to be held on March 14–16, 2011 in Seattle, WA, USA.

A broad range of topics related to health metrics and evaluation will be covered during the conference. Abstracts can be submitted on the following topics: the latest approaches to measuring maternal mortality; transitions in non-communicable diseases in rich and poor countries; controversies in the burden of malaria; trends in health inequalities; integrated surveillance systems; responsible data sharing and strengthening country capacity for analysis; new quantitative tools for priority setting; and the next generation of metrics for health-system performance. For further details on the conference programme and topics, please refer to the conference website.[1]

Abstracts should be no longer than 250–300 words in length, and written in English. Please submit abstracts online at the conference website,[1] no later than Dec 6, 2010. The peer-review process will be organised by *The Lancet*. Participants will be informed of the acceptance of abstracts for oral or poster presentation no later than Jan 24, 2011. Accepted abstracts will be published in a booklet and on *The Lancet*'s website. When relevant to the type of presentation to be made, abstracts should include the following: background/introduction, objectives, methodology, results, and conclusions/recommendations.

GHME Conference Organizing Committee

The Organizing Committee is: Zulfiqar Bhutta, Division of Women & Child Health, Aga Khan University, Karachi, Pakistan; Julio Frenk, Harvard School of Public Health, Boston, MA, USA; Richard Horton, *The Lancet*, London, UK; Alan Lopez, School of Population Health, University of Queensland, Herston, QLD, Australia; Fatima Marinho de Souza, Pan American Health Organization, Washington, DC, USA; Anne Mills, Peter Piot, London School of Hygiene & Tropical Medicine, London, UK; Christopher Murray, Institute for Health Metrics and Evaluation, Seattle, WA, USA; Osman Sankoh, INDEPTH Network, Accra, Ghana; Kenji Shibuya, Department of International Health Policy, University of Tokyo, Tokyo, Japan; and Debrework Zewdie, Global Fund to Fight AIDS, Tuberculosis and Malaria, Geneva, Switzerland

1 Institute for Health Metrics and Evaluation. Global health metrics and evaluation conference. http://www.healthmetricsandevaluation.org/GHME (accessed Oct 13, 2010).

添付資料　4

Japan-a call for research papers

Public health insecticide development: a status of hiatus

For more than 30 years, no new classes of insecticide have been introduced for wide-scale public health use. Resistance to the pyrethroids, the last class introduced (and the only class approved for use on insecticide-treated bednets [ITNs]), is seriously compromising the effectiveness of malaria-control interventions.[1] With no alternative compound in the wings, researchers have been left searching for ways to prolong the operational lifespan of pyrethroids.

In insecticide development, the public health market has traditionally played second fiddle to the far more profitable agriculture market, making do with hand-me-downs originally designed to agricultural specifications. Since the 1980s, in line with agricultural demand, insecticide development has moved away from persistence and low contact toxicity—arguably the two most important qualities for a public health insecticide—causing the pipeline of insecticides suitable for public health to dry up.

How was such a longstanding impasse in production of public health insecticides allowed? Resistance to DDT was one of the main reasons for abandonment of the Global Malaria Eradication Program in 1969. DDT and pyrethroids have a very similar mode of insecticidal action, which means mechanisms that confer resistance to one will probably confer resistance to the other. Albeit with the wisdom of hindsight, resistance to pyrethroids, and the endangerment of all the eggs in the proverbial basket, was highly likely, if not inevitable.

In 2005, in a bid to rectify this market failure, the Innovative Vector Control Consortium was set up with funding from the Bill & Melinda Gates Foundation. It was charged with re-engaging agrochemical companies and developing a portfolio of new chemicals and technologies for public health use. 5 years on, encouraging progress has been made—five new active ingredient projects are at various stages of development.[2] However, in the search for a non-pyrethroid insecticide for ITNs, many years could pass before they deliver a valid option for malaria-control programmes.

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1 Ranson H, N'Guessan R, Lines J, Moiroux N, Nkuni Z, Corbel V. Pyrethroid resistance in African anopheline mosquitoes: what are the implications for malaria control? *Trends Parasitol* 2010; published online Sept 13. DOI:10.1016/j.pt.2010.08.004.
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Japan—a call for research papers

Japan achieved universal health insurance coverage in 1961 and now has the longest life expectancy in the world.[1] Japan's strengths are, however, now becoming its weaknesses. Universal coverage is not the end but the beginning of new challenges—a rapidly ageing population, escalating health-care expenditures, and sustainability of universal coverage—that all countries will have to face in the future.[2] How can Japan reinvigorate its health system to be more sustainable and equitable?

On the occasion of the 50th anniversary of Japan's universal coverage, *The Lancet* is producing a special Series on Japan's health and health system in September, 2011. This Series is the first country Series from a developed nation, and aims to stimulate scientific debate around the issue of health-systems reform while using experiences in Japan to provide national, regional, and global lessons.

We seek submissions of original research from Japan or from research teams working on Japan, to publish in the Series. We are particularly interested in research that analyses key questions of health status, health policy, and health systems, both within Japan and within the Asia-Pacific region. The deadline for submissions is April 15, 2011, via *The Lancet*'s EES online submission system. Please state in your covering letter that the submission is in response to this call for papers.

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添付資料 5

What do we really know about adult mortality worldwide?

in 100% of patients, rather than in 40% of patients for intravenous alteplase. Indeed, for successfully recanalised endovascular-treated patients, data suggest the general upper limit for reperfusion to exert broad benefit for large artery ischaemic stroke patients is 6–7 h.[10]

An even more important message from today's pooled data lies at the other end of the time range, early after symptom onset. Although the investigators conservatively imposed a linear relation on the interaction between onset to start of treatment and good outcome, their tabular data suggest the relation is probably more an exponential decay (figure). Although odds ratios might overestimate effect size (compared with relative risk) when outcomes are common, the odds of favourable outcome seem to drop more precipitously in the first 90-min window (36%), moderately in the second (18%), and mildly in the third (9%)—essentially dropping off by a factor of two in each 90-min period.

These findings mandate a renewed commitment by clinicians and policy makers to foster very early intervention.[11,12] We need to increase the proportion of patients arriving at hospital in the first, golden hour after ischaemia onset by better educating the public to recognise stroke warning signs and activate the emergency medical system at the first sign of potential stroke, training prehospital personnel to scoop and go, having field personnel provide prearrival notification to receiving centres, and by routing ambulances carrying possible stroke patients directly to designated stroke centres. Moreover, stroke centres should target the improvement of hospital-response systems to achieve door-to-needle times of less than 60 min in the great majority of patients treated with intravenous alteplase. In thrombolytic stroke therapy, sooner is better than later, much better.

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JLS is an employee of the University of California, which holds a patent on retriever devices for stroke; is a scientific consultant regarding trial design and conduct to Concentric Medical, Talecris, and Ev3; has received lecture honoraria from Boehringer Ingelheim; has been a site investigator in multicentre trials sponsored by Vernalis, Paion, Lundbeck, and Neurobiological Technologies, for which the University of California Regents received payments based on the clinical trial contracts for the number of subjects enrolled; is a site investigator in the NIH IRIS, CLEAR, IMS 3, SAMMPRIS, and VERITAS multicentre clinical trials, for which the University of California Regents receive payments based on the clinical trial contracts for the number of subjects enrolled; is a lead investigator in the NIH MR RESCUE multicentre trial; and is funded by NIH-NINDS Awards P50 NS044378 and U01 NS 44364. SRL has been an investigator for an NIH-funded trial of tenecteplase, manufactured by Genentec; has received an honorarium from the National Stroke Association for a webcast; and is funded by NIH-NINDS Awards R01 NS052417, R01 HL096944, U01 NS044364, and T32 NS051147. He is the independent medical monitor for NIH clinical trials IMS 3, CLEAR-ER, FAST-MAG, and INSTINCT.

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What do we really know about adult mortality worldwide?

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As child mortality continues to decline globally, more children survive to adulthood, and it is imperative to prevent premature deaths in adults. But what do we really know about how many adults aged between 15 and 60 years—the most healthy and productive age group in our society—are dying today?

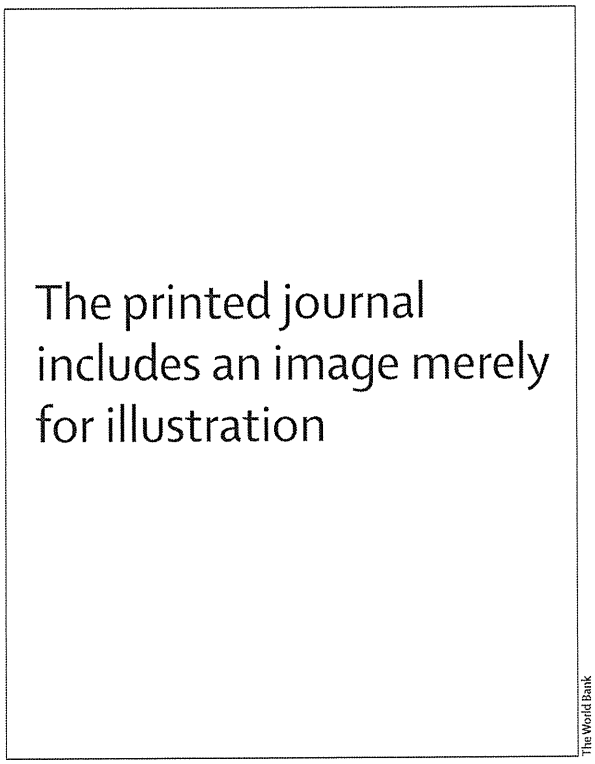
Despite the growing interest in the health of adults over the past two decades since the publication of the *World development report 1993: investing in health*,[1] a rigorous assessment of the levels and trends of adult mortality has been neglected, partly due to the huge measurement challenge (ie, adult deaths are rare events

compared with deaths in children) and the preference of donors to focus on disease-specific adult mortality estimates which cannot be consistent without all-cause adult mortality. With only 5 years left to achieve the Millennium Development Goals (MDGs), which include a subset of adult mortality, the global health community is in dire need of data to monitor progress in health-related MDGs and evaluate the impact of global health initiatives.

So what do we have? An abundance of incomplete data on adult mortality—only 26% of the world's population lives in countries with a complete civil registration system.[2] This incompleteness has rendered the modelling of adult mortality painstakingly difficult. To date, UN agencies, such as the UN Population Division and WHO, have relied on existing models which extrapolate adult mortality from child mortality[3,4] and which suffer from well known weaknesses especially in the era of HIV/AIDS. Furthermore, ambiguity remains in the source of data and underlying methods that yielded the estimates, thereby impeding replication of results.[3,4]

In *The Lancet* today, Julie Rajaratnam and colleagues[5] have tackled the difficulties of estimating adult mortality and provide detailed assessment of the levels and trends of adult mortality for the past four decades. At least three major breakthroughs should be noted in this landmark study. First, the investigators substantially improved the existing method of adult mortality estimation.[6,7] They made optimum use of available data, including incomplete or indirect empirical data on adult mortality, thereby allowing inclusion of a fairly large amount of new information in their estimation that was not included in previous UN assessments. Second, they used a method that generates the most likely substitute for missing data. In particular, they developed a new approach with high predictive validity to incorporate variation over time and across countries when estimating trends. Third, and perhaps most importantly, their approach is more transparent and replicable than previously published UN estimates on adult mortality.

Rajaratnam and colleagues comprehensively showed the diverse patterns of adult mortality across countries and changing trends. Because much of the variation in adult mortality cannot be explained by the combination of economic development, the HIV epidemic, and child mortality, the new analysis challenges the common theories behind health transition,[8] which will stimulate debates on alternative theories and the roles of social determinants, health systems, and medical technologies.



The method developed by Rajaratnam and colleagues is promising but is not our final goal. Without empirical measurements, knowledge on the levels and trends of adult mortality will still be haunted by ambiguity and uncertainty. For the past few years, the large discrepancy between the estimates published by UN agencies, notably WHO and UNICEF, and third parties in MDG 4 (child mortality) and 5 (maternal mortality) has been puzzling and frustrating the global health community,[9,10] which is now likely to spread to adult mortality. The impact of the global initiative to achieve MDG 6 relies heavily on cause-specific mortality data from major diseases such as HIV/AIDS and tuberculosis, but contradicting estimates will have a profound negative effect on the global health community, including beneficiaries of health programmes, countries, and policy makers.

This new modelling method by Rajaratnam and colleagues is a powerful monitoring tool for adult mortality with incomplete data while countries progress towards establishment of a sustainable civil-registration system.[6] All-cause adult mortality and causes of death are a must. The combination of these two will be invaluable in health-policy decision making irrespective of the

country's economic situation. Even in the most resource-limited setting, information on levels and causes of death can be obtained by standardised household surveys with modules on sibling survival and verbal autopsy.[7,11] In view of the multitude of existing household surveys in developing countries and a potential way of joint funding by the GAVI Alliance, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the World Bank in monitoring and evaluation at country level,[12] empirical data collection is now feasible, for which the UN agencies could play a crucial role through the UN's convening power and standard-setting roles. Only with a strong leadership, together with technical integrity among those involved in the process of scientific debates, will the global health community become confident with what works and what does not in achieving the health-related MDGs.

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Light-chain MGUS: implications for clinical practice

See Articles page 1721

Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant condition defined by the presence of a serum monoclonal protein (M-protein) of less than 3 g/dL with less than 10% monoclonal plasma cells in bone marrow in the absence of hypercalcaemia, renal insufficiency, anaemia, or skeletal lytic lesions.[1] Prevalence was 3·2% in a population-based survey of 21 000 residents aged 50 years or older in Olmsted County, Minnesota, USA.[2] Prevalence increased with age and reached 7·5% in individuals aged 85 years or older. Examination of the discharge records of 142 Veteran Affairs hospitals between 1980 and 1996 revealed that MGUS was three times more common in African-Americans than in white veterans.[3] Several studies have shown that the rate of progression of MGUS to multiple myeloma or related disorders is about 1% per year and remains constant over time.[4]

A nationwide cancer screening study prospectively enrolled nearly 77 500 healthy adults aged 55–74 years, of whom 71 developed multiple myeloma.[5] Analysis of stored blood samples dating back 2–8 years before the diagnosis of multiple myeloma revealed the presence of an M-protein in all patients, which suggests that multiple myeloma invariably evolves from MGUS. However, it cannot be excluded that some patients might have had undiagnosed multiple myeloma. In a second study of stored samples from the US Department of Defense Serum Repository, M-protein was detected before diagnosis of multiple myeloma in 27 of 30 patients, which lends further support to the hypothesis that an MGUS state precedes overt multiple myeloma.[6] Both studies found a small number of patients in whom light chains only were detected without a corresponding immunoglobulin heavy protein by serum assay of free light chain. The existence of light-chain MGUS was suspected from as early as 1982 with the description of idiopathic Bence-Jones proteinuria, a disease entity that might represent a more advanced stage of light-chain MGUS.[7] Further, with the advent of the highly sensitive free-light-chain assay, light-chain MGUS has been seen occasionally in every major referral centre for multiple myeloma.

添付資料　6

Designing Verbal Autopsy Studies Population Health Metrics

King et al. Population Health Metrics 2010, 8:19
http://www.pophealthmetrics.com/content/8/1/19

POPULATION HEALTH METRICS

RESEARCH Open Access

Designing verbal autopsy studies

Gary King[1*], Ying Lu[2], Kenji Shibuya[3]

Abstract

Background: Verbal autopsy analyses are widely used for estimating cause-specific mortality rates (CSMR) in the vast majority of the world without high-quality medical death registration. Verbal autopsies – survey interviews with the caretakers of imminent decedents – stand in for medical examinations or physical autopsies, which are infeasible or culturally prohibited.

Methods and Findings: We introduce methods, simulations, and interpretations that can improve the design of automated, data-derived estimates of CSMRs, building on a new approach by King and Lu (2008). Our results generate advice for choosing symptom questions and sample sizes that is easier to satisfy than existing practices. For example, most prior effort has been devoted to searching for symptoms with high sensitivity and specificity, which has rarely if ever succeeded with multiple causes of death. In contrast, our approach makes this search irrelevant because it can produce unbiased estimates even with symptoms that have very low sensitivity and specificity. In addition, the new method is optimized for survey questions caretakers can easily answer rather than questions physicians would ask themselves. We also offer an automated method of weeding out biased symptom questions and advice on how to choose the number of causes of death, symptom questions to ask, and observations to collect, among others.

Conclusions: With the advice offered here, researchers should be able to design verbal autopsy surveys and conduct analyses with greatly reduced statistical biases and research costs.

Introduction

Estimates of cause-specific morality rates (CSMRs) are urgently needed for many research and public policy goals, but high quality death registration data exists in only 23 of 192 countries [1]. Indeed, more than two-thirds of deaths worldwide occur without any medical death certification [2]. In response, researchers are increasingly turning to verbal autopsy analyses, a technique "growing in importance" [3]. Verbal autopsy studies are now widely used in the developing world to estimate CSMRs, disease surveillance, and sample registration [4-6], as well as risk factors, infectious disease outbreaks, and the effects of public health interventions [7-9].

The idea of verbal autopsy analyses is to ask (usually around 10-100) questions about symptoms (including some signs and other indicators) of the caretakers of randomly selected decedents and to infer from the answers the cause of death. Three approaches have been used to draw these inferences. We focus on the fourth and newest approach, by King and Lu, which requires many fewer assumptions [10]. We begin by summarizing the main existing approaches. We then discuss our main contribution, which is in the radical new (and much easier) ways of writing symptom questions, weeding out biased symptoms empirically, and choosing valid sample sizes.

The first is *physician review*, where a panel of (usually three) physicians study the reported symptoms and assign each death to a cause, and then researchers total up the CSMR estimates [11]. This method tends to be expensive, time- consuming, unreliable (in the sense that physicians disagree over a disturbingly large percentage of the deaths), and incomparable across populations (due to differing views of local physicians); in addition, the reported performance of this approach is often exaggerated by including information from medical records and death certificates among the symptom questions, which is unavailable in real applications [12]. The second approach is *expert systems*, where a decision tree is constructed by hand to formalize the best physicians'

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judgments. The result is reliable but can be highly inaccurate with symptoms measured with error [13,14].

The third approach is *statistical classification* and requires an additional sample of deaths from a medical facility where each cause is known and symptoms are collected from relatives. Then a parametric statistical classification method (e.g., multinomial logit, neural networks, or support vector machines) is trained on the hospital data and used to predict the cause of each death in the community [15]. These methods are unbiased only if one of two conditions hold. The first is that the symptoms have 100% sensitivity and specificity. This rarely holds because of the inevitable measurement error in survey questions and the fact that symptoms result from rather than (as the predictive methods assume) generate the causes that lead to death. A second condition is that the symptoms represent all predictive information and also that everything about symptoms and the cause of death is the same in the hospital and community (technically, the symptoms span the space all predictors of the cause of death and the joint distribution of causes and symptoms are the same in both samples [16]). This condition is also highly unlikely to be satisfied in practice.

Like statistical classification, the King-Lu method [10] is data-derived and so requires less qualitative judgment; it also requires hospital and community samples, but makes the much less restrictive assumption that only the distribution of symptoms for a given cause of death is the same in the hospital and community. That is, when diseases present to relatives or caregivers in similar ways in the hospital and community, then the method will give accurate estimates of the CSMR. This is true even when the symptom questions chosen have very low (but nonzero) sensitivity and specificity, when these questions have random measurement error, when the prevalence of different symptoms and the CSMR differ dramatically between the hospital and community, or if the data from the hospital are selected via case-control methods. Case-control selection, where the same number of deaths are selected in the hospital for each cause, can save considerable resources in conducting the survey, especially in the presence of rare causes of death in the community. The analysis (with open source and free software) is easy and can be run on standard desktop computers. In addition, so long as the symptoms that occur with each cause of death do not change dramatically over time (even if the prevalence of different causes do change), the hospital sample can be built up over time, further reducing the costs.

Conceptually, the King-Lu method involves four main advances (see Appendix A for a technical summary). First, King-Lu estimates the CSMR, which is the main quantity of interest in the field, rather than the correct classification of any individual death. The method generates unbiased estimates of the CSMR even when the percent of individual deaths that can be accurately classified is very low. (The method also offers a better way to classify individual deaths, when that is of interest; see Appendix A and [[10], Section 8].) Second is a generalization to multiple causes of the standard "back calculation" epidemiological correction for estimating the CSMR with less than perfect sensitivity and specificity [17,18]. The third switches "causes" and "effects" and so it properly treats the symptoms as consequences rather than causes of the injuries and diseases that lead to death. Since symptoms are now the outcome variables, it easily accommodates random measurement error in survey responses. The final advance of this method is dropping all parametric modeling assumptions and switching to a fully nonparametric approach. The result is that we merely need to tabulate the prevalence of different symptom profiles in the community and the prevalence of different symptom profiles for each cause of death in the hospital. No modeling assumptions, not much statistical expertise, and very little tweaking and testing are required to use the method.

Building on [10], we now develop methods that minimize statistical bias in Section and inefficiency in Section 0.4 by appropriately choosing symptom questions, defining causes of death, deciding how many interviews to conduct in the hospital and community, and adjusting for known differences between samples. Software to estimate this model is available at http://gking.harvard.edu/va.

Avoiding Bias

[10] indicates how to avoid bias from a statistical perspective. Here, we turn these results and our extensions of them into specific, practical suggestions for choosing survey questions. We do this first via specific advice about designing questions (Section 0.1), then in a section that demonstrates the near irrelevance of sensitivity and specificity, which most previous analyses have focused on (Section 0.2), and finally via a specific method that automates the process of weeding out questions that violate our key assumption (Section 0.3).

0.1 Question Choice

The key to avoiding bias is ensuring that patients who die in a hospital present their symptoms in the verbal autopsy survey instrument (as recorded by relatives and caregivers) in the same way as do those in the community (or in other words that the assumption in Equation 3 holds). As such, it may seem like the analyst is at the mercy of the real world: either diseases present the same way in the two locations or they do not. In fact, this is not the case, as the analyst has in the choice of

symptom questions a powerful tool to reduce bias. In other words, how the patient presents symptoms to relatives and caregivers is only relevant inasmuch as the analyst asks about them. That means that avoiding bias only requires not posing symptom questions likely to appear different to those in the two samples (among those who cared for people dying of the same cause).

For an example of a violation of this assumption, consider that relatives of those who died in a medical facility would be much more likely than their counterparts in the community to know if the patient under their care suffered from high blood pressure or anemia, since relatives could more easily learn these facts only from medical personnel in a hospital than in the community without proper ways of measuring these quantities. Avoiding questions like these can greatly increase the accuracy of estimates. In contrast, the respondent noting whether they observed the patient bleeding from the nose would be unlikely to be affected by a visit to a hospital, even under instruction from medical personnel.

This fundamental point suggests avoiding any symptom questions about concepts more likely to be known by physicians and shared with patients or taught to caregivers than known by those in the community who were unlikely to have been in contact with medical personnel. We should therefore be wary of more sophisticated, complicated, or specialized questions likely to be answerable only by those who have learned them from medical personnel. The questions a relative is even likely to understand and answer accurately are not those which a physician might determine from a direct physical examination. *Trying to approximate the questions physicians ask themselves is thus likely to lead* to bias. In contrast, finding questions respondents are easily able to answer, and likely to give the same answers despite their experience in a medical facility, is best.

It is important to understand how substantially different these recommendations are from the way most have gone about selecting verbal autopsy survey questions. Most studies now choose questions intended to have the highest possible sensitivity and specificity. At best, this emphasis does not help much, because they are not required for accurate CSMR inferences, a point we demonstrate in the next section. However, this emphasis can also lead to huge biases when symptom questions with highest sensitivity and specificity are those that are closest to questions physicians would ask themselves, medical tests, or other facts which relatives of the deceased learn about about when in contact with medical personnel. (A related practical suggestion for reducing bias is to select a hospital as similar as possible to the community population. In most cases, physical proximity to large portions of the community will be helpful, but the main goal should be selecting a medical facility which has patients that present their symptoms in similar ways in hospital as in the community for each cause of death.)

0.2 The Near Irrelevance of Sensitivity and Specificity

Verbal autopsy researchers regularly emphasize selecting symptom questions based on their degree of sensitivity and specificity. It is hard to identify a study that has selected symptom questions in any other way, and many criticize verbal autopsy instruments for their low or variable levels of sensitivity and specificity across data sets and countries. This emphasis may be appropriate for approaches that use statistical classification methods, as they require 100% sensitivity and specificity, but such stringent and unachievable requirements are not needed with the King-Lu approach. We now provide evidence of this result.

We begin by generating data sets with 3,000 sampled deaths in the community and the same number in a nearby hospital (our conclusions do not depend on the sample size). The data consist of answers to 50 symptom questions – which we use in subsets of 20, 30, and 50 – and 10 causes of death. Because we generated the data, we know both the answers to the symptom questions and the cause of death for everyone in both samples; however, we set aside the causes of death for those in the community, which we ordinarily would not know, and use them only for evaluation after running each analysis.

We first generate a "high sensitivity" symptom, which we shall study the effect of. It has 100% sensitivity for the first cause of death and 0% for predicting any other cause of death (i.e., it also has high specificity). (The prevalence of this first cause of death is 20% overall.) Every other symptom has a maximum of 30% sensitivity for any cause of death. For each of 20, 30, and 50 symptoms, we generate 80 data sets with and without this high sensitivity symptom (each with 3,000 samples from the hospital and 3,000 from the community). In each data set, we estimate the CSMR. We then average over the 80 results for each combination of symptoms and compare the average of these estimates to the truth. This averaging is the standard way of setting aside the natural sampling variability and focusing on systematic patterns.

The results appear in Table 1, with different numbers of symptoms given in separate columns. The first two rows of the table give the difference in the proportion of deaths estimated to be in the first category with (for the first row) and without (for the second) the high sensitivity symptom. Clearly the difference between the numbers in the first two rows is trivial, indicating the near irrelevance of including this symptom. The second pair of rows in the table give the absolute error in estimating

Table 1 Absolute error rates with and without a symptom that has very high sensitivity for the first cause of death

	Number of Symptoms		
	20	30	50
Absolute Error for First Cause of Death			
With high sensitivity symptom	0.0128	0.0120	0.0123
Without high sensitivity symptom	0.0128	0.0124	0.0124
Mean Absolute Error			
With high sensitivity symptom	0.0090	0.0081	0.0084
Without high sensitivity symptom	0.0092	0.0082	0.0085

The first and second row of each pair are very similar, which illustrates the irrelevance of finding symptoms with high sensitivity.

the effects for all causes of death. Again, the results show the irrelevance of including this high sensitivity symptom. (The numbers in the tables are proportions, so that 0.0128 represents a 1.28 percentage point difference between the estimate and the truth.)

Searching for high sensitivity symptoms is thus at best a waste of time. The essential statistical reason for this is that symptoms do not cause the diseases and injuries that result in death. Instead, the symptoms are consequences of these diseases and injuries. As such, assessing whether the symptoms have high sensitivity and specificity for predicting something they do not predict (or cause) in the real world, and are not needed to predict with the method, is indeed irrelevant.

The King-Lu method works by appropriately treating symptoms as consequences of the disease or injury that caused death. Even if they were available, having symptoms that approximate highly predictive bioassays is neither necessary nor even very helpful. Any symptom which is a consequence of one or more of the causes of death can be used to improve CSMR estimates, even if it has random measurement error. So long as a symptom has some, possibly low-level, relationship to the causes of death, it can be productively used. Even apparently tertiary, behavioral, or non-medical symptoms that happen to be consequences of the illness can be used so long as they are likely to be reported in the same way regardless of whether the death occurred in a hospital or the community.

0.3 Detecting Biased Symptom Questions

Suppose we follow the advice offered on selecting symptom questions in Section 0.1, but we make a mistake and include a question which unbeknownst to us induces bias. An example would be a symptom which, for a given cause of death, is overreported in the hospital vs the community. Appendix B shows that in some circumstances it's possible to detect this biased symptom question, in which case we can remove it and rerun the analysis without the offending question. Since many verbal autopsy instruments include a large number of questions, this procedure could be used to eliminate questions without much cost. In this section, we present analyses in simulated and real data that demonstrate the effectiveness of this simple procedure.

We thus conduct a simulations where different numbers of symptom questions are "misreported" – that is, reported with different frequencies in the hospital and community samples for given causes of death. We generate two sets of data, one with 3,000 deaths in each of the hospital and community samples and the other with 500 deaths in each; both have 10 different causes of death, with distribution D = (0.2, 0.2, 0.2, 0.1, 0.05, 0.05, 0.05, 0.05, 0.05, 0.05). The CSMF distribution of D in the hospital is uniform (0.1 for each cause) and in the community is D = (0.2, 0.2,..., 0.2, 0.05). Table 2 summarizes the pattern of misreporting we chose. In this table, the first row indicates which symptom number is to be set up as misreported when applicable. The second row gives the extent of the violation of the key assumption of the King-Lu method (in Equation 3) – the percentage point difference between the symptom's marginal distribution in the community and hospital samples. For example, where three symptoms are misreported, we generate data using the first three columns of Table 2 and so the marginal prevalence of the first, fifth, and 10th symptoms in the community sample are set to be different from the hospital according to the first three elements of the second column. When five symptoms are misreported, the distribution of the first, fifth, 10th, 11th and 15th symptoms will be set to be different in the degree as indicated, etc.

We first give our large sample and small sample results and then give a graphic illustration of the bias-efficiency trade-offs involved in symptom selection.

Larger Sample Size

For the large (n = 3, 000) simulation, Table 3 summarizes the results of symptom selection for each different simulation. The first two columns indicate, respectively, the total number of symptoms and the number of biased symptoms included in the community sample. The third column indicates the number of symptoms flagged (at the 5% significance level), using the selection procedure proposed in Appendix B. The final column indicates the number of biased symptoms that are correctly identified.

Table 3 indicates that our symptom selection procedure is highly accurate. Except the first simulation, which has disproportionately many misreported

Table 2 List of Misreported Symptoms

Symptom	1	5	10	11	15	20	21	25	30	31
Misreport	30%	-30%	-50%	30%	-30%	30%	-30%	-50%	30%	-30%

Table 3 Performance of the Symptom Selection Method with n = 3, 000

symptoms	biased	flagged	correct
10	3	0	0
20	3	3	3
30	3	3	3
50	3	3	3
20	5	5	5
30	5	5	5
50	5	6	5
50	10	10	10

symptoms (three out of 10), our proposed method correctly selects nearly all the biased symptoms. There is only one false positive case, but if we were to change the joint significance level to 0.01, this symptom would no longer being incorrectly selected.

Smaller Sample Size

Our smaller (n = 500) simulation necessarily results in larger CSMR variances. This, in turn, affects the power of the method described in Appendix B to detect biased symptoms. And at the same time it makes it more costly to discard unbiased symptoms. As shown in Table 4, we miss some symptoms at the 5% level. If we relax the type I error rate to 10%, more biased symptoms are detected. The table also conveys the additional variation in our methods due to the smaller sample size.

Bias-Efficiency Trade-offs

Although these results are encouraging, in real-world data, a trade-off always exists between choosing a lower significance level to ensure that all biased symptoms are selected at a cost of increasing the false positive rate, vs. choosing a higher significance level to reduce the false positive rate at the cost of missing some biased symptoms. In this section, we illustrate how different sample sizes can affect the decision about the significance level in practice.

We now choose "large" (3, 000), "medium" (1, 000), and "small" (500) samples for each of the community and hospital samples. In each, 10 of 50 symptoms are biased. We then successively remove symptoms all the way up to the 50% signficance level criterion (to see the full consequence of dropping too many symptoms). Figure 1 gives the results in a graph for each sample size separately, (large, medium, and small sample sizes from left to right). Each graph then displays the mean square error (MSE) between the true and estimated cause-of-death distribution for each run of the model vertically, removing more and more symptoms as from the left to the right along the horizontal axis of each graph. (In real applications, we would never be able to compute the MSE, because we do not observe the true cause of death, but we can do it here for validation because the data are simulated.) That is, all symptoms are included for the first point on the left, and each subsequent point represents a model estimated with an additional symptom dropped, as selected by our procedure. Circles are plotted for models where a biased symptom was selected and solid disks are plotted for unbiased symptoms.

Table 4 Performance of the Symptom Selection Method with n = 500

		5% error rate		10% error rate	
symptoms	biased	flagged	correct	flagged	correct
10	3	0	0	1	1
20	3	3	3	3	3
30	3	2	2	5	3
50	3	3	3	5	3
20	5	2	2	3	3
30	5	3	3	4	4
50	5	4	4	4	4
50	10	6	3	6	3

Three key results can be seen in this figure. First, for all three sample sizes and corresponding graphs, all biased symptoms are selected before any unbiased symptoms are selected, without a single false positive (which can be seen because all circles appear to the left of all solid disks).

Second, all three figures are distinctly U-shaped. The reason can be seen beginning at the left of each graph with a sample that includes biased symptoms. As our selection procedure detects and deletes these biased symptoms one at a time, the MSE drops due to the reduction in bias of the estimate of the CSMR. Dropping additional symptoms after all biased ones are dropped, which can occur if the wrong significance level is chosen, will induce no bias in our results but can reduce efficiency. If few unbiased symptoms are deleted, little harm is done since most verbal autopsy data sets have many symptoms and so enough efficiency to cover the loss. However, if many more unbiased symptoms are dropped, the MSE starts to increase because of inefficiency, which explains the rest of the U-shape.

Finally, in addition to choosing the order in which symptoms should be dropped, our automated selection procedure also suggests a stopping rule based on the user-choice of a significance level. The 5% and 10% significance level stopping rules appear on the graphs as solid and dashed lines. These do not appear exactly at the bottom of the U-shape, cleanly distinguishing biased from unbiased symptoms, but for all three sample sizes the results are very good. In all cases, using this stopping rule would greatly improve the MSE of the ultimate estimator. Our procedure thus seems to do work reasonably well.

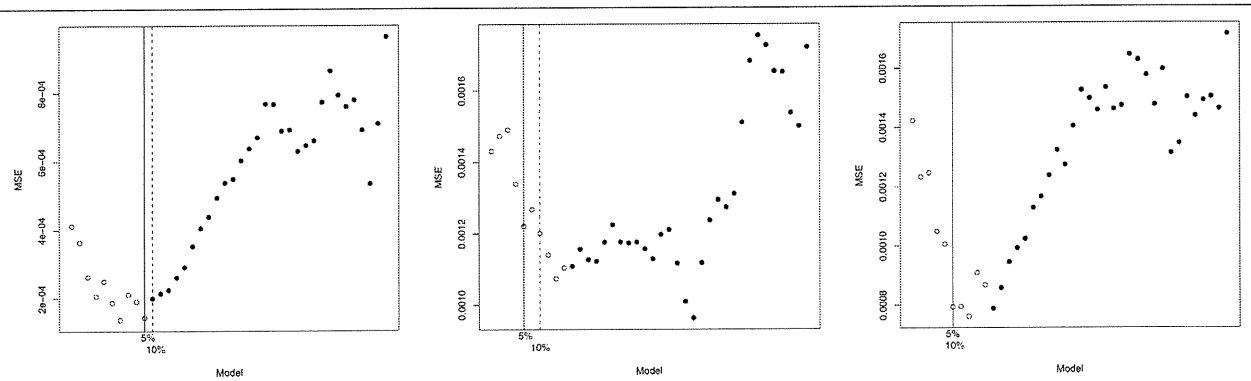

Figure 1 For sample sizes of 3,000 (left graph), 1,000 (middle), and 500 (right), the figure gives the mean square error as symptoms are removed using our detection diagnostic. The mean square error first declines, as bad symptoms are removed and bias drops, and then increases, as unbiased symptoms are dropped and variance increases. The procedure selects all biased symptoms (open circles) before unbiased symptoms (solid disks). The vertical line indicates where our automated procedure would indicate that we should stop.

Empirical Evidence from Tanzania

Finally, we apply the proposed validation method to a real data example where we happen to observe the true causes of death in both samples [19]. These data from Tanzania have 12 causes of death and 51 symptoms questions but a small sample of only 282 deaths in the community sample and 1,261 in the hospital. Applying our symptom selection method, at the 5% level, four symptoms would be deleted, which in fact corresponds to the smallest MSE along the iterative model selection process. Figure 2 gives these results.

To illustrate this example in more details, Table 5 shows how the mean square error changes when specific symptoms were sequentially selected, And in Table 6 we present the change in each cause-specific mortality fraction estimate as these four symptoms are sequentially removed.

The first three symptoms which were sequentially dropped – fever, pale, and confused – are so non-specific that they were almost unable to distinguish all of the 12 causes clinically, with the possible exception of deaths from injuries. Although high levels of specificity are not necessary for our method, we do require that it is above zero. Wheezing is a distinctive clinical symptom of an airway obstruction, typically observed in patients with asthma or bronchitis, and would be useful to identify deaths from such causes. However, our method suggests that it was highly biased. In fact,

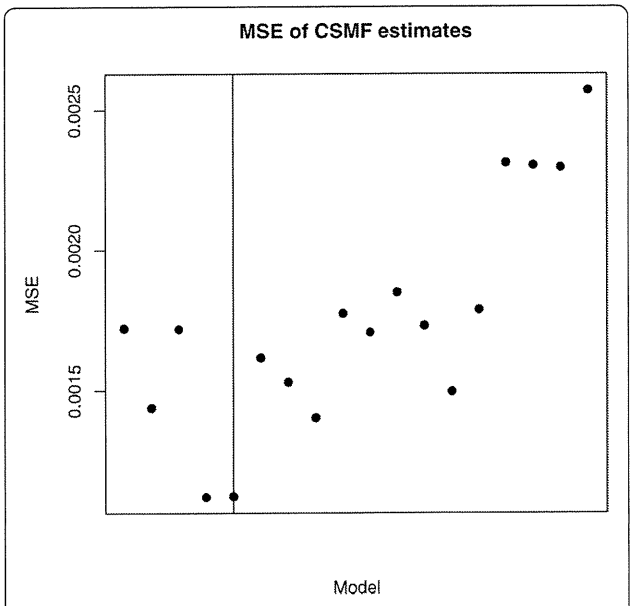

Figure 2 Validation of Mean Square Error in Tanzania, where the true cause of death is known in both samples.

Table 5 List of symptoms that are sequentially removed from the analysis

	prevalence		
symptoms	hospital	community	mean square error
-	-	-	0.0016
fever	72.6	45.4	0.0013
pale	33.1	17.4	0.0018
confused	30.8	14.5	0.0012
wheezing	8.3	21.3	0.0012
vomit	49.0	35.5	0.0015
difficult-swallow	18.9	7.4	0.0015
diarrhoea	29.8	20.9	0.0014
chest-pain	43.9	33.0	0.0017
pins-feet	14.6	8.5	0.0015
many-urine	8.4	5.3	0.0016
breathless-flat	28.2	35.5	0.0015
pain-swallow	15.5	6.7	0.0015
mouth-sores	22.7	13.8	0.0018
cough	50.0	38.7	0.0020
body-stiffness	6.9	2.5	0.0021
puffiness-face	11.7	11.3	0.0025
breathless-light	34.9	33.3	0.0027