the Institutional Review Board of St Joseph's Hospital, Tampa, Florida, USA.

Under general anesthesia the bladder of the fetus was accessed percutaneously under ultrasound guidance with a 3·5 mm trocar. Fetal cystoscopy showed a cecoureterocele extending from the right side of the bladder floor (bladder neck) to the urethra (figure). The ureterocele was incised without complications with a neodymium:yttrium-aluminium-garnet laser (Surgical Laser Technologies, Montgomeryville, PA, USA) using a 400 μm contact fibre both at the level of the urethra and bladder, with immediate decompression of the lesion.

Postoperatively, restoration of the amniotic fluid was monitored, and the pregnancy progressed uneventfully. The bladder decreased in size within 24 h from 6·4 cm to 3 cm, to 1·9 cm 3 weeks later, and to 1·5 cm at 5 weeks postoperatively. The left renal pelvis also decreased from 8 mm to 4·1 mm in width within 24 h of the operation. The right ureterovesical junction was also smaller, measuring 1·3 cm preoperatively and 0·68 cm postoperatively. Spontaneous delivery of a healthy 2835 g infant occurred at 36 weeks and 6 days. Postnatal urological assessment with diuretic technetrium-99m mertiatide renography disclosed a normal left kidney (normal urinary function) and a non-functioning right kidney. Voiding cystourethrography showed massive grade 5 reflux into a duplex right kidney with megaureters. The baby underwent a right nephrectomy and is currently doing well.

We describe a case of in-utero treatment of fetal obstructive ureterocele. Indications for fetal surgery included progressive bladder outlet obstruction with increasing megacystis and oligohydramnios as well as dilatation of the ureter. Access to the fetal bladder was gained as previously described.[5] As a result of the treatment amniotic fluid volume increased, pregnancy proceeded until term, left kidney function was preserved, and pulmonary hypoplasia from oligohydramnios was avoided. Unfortunately, right kidney function could not be preserved. Earlier intervention in future cases may be warranted, but only in cases where bladder-outlet obstruction and oligohydramnios are present. Prenatal treatment of bladder-outlet obstructing fetal ureterocele constitutes another landmark in minimally-invasive fetal therapy, expanding the applications of this approach for the in-utero correction of birth defects. The value and limitations of this novel prenatal intervention are yet to be proved.

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Florida Institute for Fetal Diagnosis and Therapy, St Joseph's Hospital, Tampa, Florida, USA (R A Quintero MD, Y Homsy MD, P W Bornick RN, M Allen RN, P K Johnson RDMS)

Correspondence to: Dr Rubén A Quintero, 13601 Bruce B Downs Boulevard, Suite 160 Tampa, FL 33613, USA (e-mail: yvrq@aol.com)

Fake artesunate in southeast Asia

Paul Newton, Stephane Proux, Michael Green, Frank Smithuis, Jan Rozendaal, Sompol Prakongpan, Kesinee Chotivanich, Mayfong Mayxay, Sornchai Looareesuwan, Jeremy Farrar, Francois Nosten, Nicholas J White

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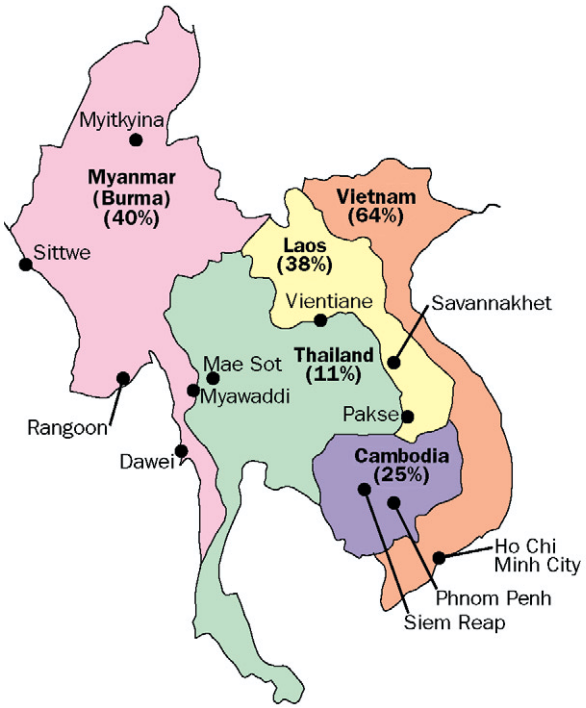
Artesunate is a key antimalarial drug in the treatment of multidrug-resistant *Plasmodium falciparum* malaria in southeast Asia. We investigated the distribution of counterfeit artesunate tablets by use of the validated, simple, and inexpensive Fast Red TR dye technique. We also aimed to identify distinguishing characteristics of the fake drugs. Of 104 shop-bought "artesunate" samples from Cambodia, Laos, Myanmar (Burma), Thailand, and Vietnam, 38% did not contain artesunate. Characteristics such as cost and physical appearance of the tablets and packaging reliably predicted authenticity. The illicit trade in counterfeit antimalarials is a great threat to the lives of patients with malaria. The dye test will assist national malaria control authorities in urgently needed campaigns to stop this murderous trade.

Artesunate, in combination with slower acting antimalarials, is the recommended treatment for *Plasmodium falciparum* malaria in much of southeast Asia, and is pivotal in areas of multidrug resistance.[1] The recent emergence of counterfeit artesunate in this region has led to the death of many patients who would have survived if given the genuine drug.[2] In response, a simple, inexpensive, and reliable dye test was developed to distinguish genuine from fake artesunate. The test is based on the reaction between an alkali-decomposition product of artesunate and the diazonium salt, (Fast Red TR).[3]

Between August, 1999, and August, 2000, we collected samples of artesunate from shops, pharmacies, non-government organisations, and hospitals in Myanmar, Cambodia, Vietnam, Laos, and western Thailand to establish the prevalence of fakes and to identify surrogate markers of drug authenticity. We used the dye test to check for the presence of artesunate, and one observer (who was unaware of the results of the dye test) examined some of the packages



Location and proportion of fake artesunate samples collected

Area/criteria	Sensitivity	Specificity	NPV	PPV
Mainland southeast Asia				
Guilin Pharma artesunate with "AS" logo on only one tablet face	100	73	1·00	0·69
Tablet heavier than 0·27 g	85	33	0·78	0·44
Unclear barcode printing	88	97	0·95	0·93
Unclear blisterpack printing	75	100	0·93	1·00
Myanmar (Burma)				
No hologram on artesunate manufactured after 1998	100	1001·00	1·.00	
No Myanmar registration number on packet	100	31	1·00	0·47
Guilin Pharma artesunate costing ⩽200 kyat per blisterpack	92	100	0·95	1·00
Crimped code on blisterpack	83	100	0·91	1·00
Six-digit manufacturing and expiry date codes on blisterpack	50	100	0·77	1·00
Cambodia* and Vietnam				
Guilin Pharma artesunate costing ⩽1500 rials per blisterpack*	100	100	1·00	1·00
Forged hologram	100	100	1·00	1·00
Date of manufacture before 1999	100	11	0·41	1·00

Prevalence of fake artesunate assumed to be 38%. NPV=negative predictive value, PPV=positive predictive value.

Summary of predictors of counterfeit artesunate

for holograms, bar codes, printing, and crimping (the impression of text into foil), classifying the sample as either genuine or fake. The tablets were also examined for colour, size, weight, consistency, and taste.

We obtained 104 samples of blisterpacks purporting to contain artesunate tablets: 51 from Myanmar, 26 from Cambodia, 11 from Vietnam, eight from Laos, and eight from western Thailand. Most samples (95 [91%]) were labelled as manufactured by Guilin Pharma (China), or repackaged by Atlantic Pharmaceuticals (Bangkok, Thailand). Overall, 30 (29%) of the blisterpacks collected contained no artesunate. All were supposedly manufactured by Guilin Pharma—the major producer of artesunate in Asia. Of the artesunate samples bought from pharmacies and shops, 39 (38%) were counterfeit. Fakes were found in all five countries (figure). The results of examining the packaging of 84 samples gave complete agreement with the dye test.

Fake artesunate tablets were superficially similar in colour, size, and inscription but were heavier than the genuine tablets (table). Genuine Guilin Pharma tablets were more friable than the fakes and had a chalky taste, whereas counterfeit artesunate tablets sometimes had a disagreeable bitter taste. In south east Asia antimalarials are traditionally bitter and chloroquine, which is largely ineffective against *P falciparum* prevelant in the region, may have been added to give a spurious taste of authenticity. Fakes labelled as the Guilin Pharma product were substantially cheaper than their genuine counterparts; fakes cost about 30% and 45% of the local price of the genuine artesunate in Cambodia and Myanmar, respectively. There were forged holograms on fake artesunate blisterpacks bought in Vietnam and Cambodia; those from elsewhere had no hologram. The holograms were distinctive, with a crude, hand-tooled design lacking the multicoloured, refractile appearance of the genuine Guilin holograms. Digital photographs are available from the authors. In terms of negative predictive value (ie, minimisation of false negatives), the most reliable surrogate marker of fake Guilin Pharma artesunate in southeast Asia overall was the presence of the "AS" logo on only one tablet face (table). The most reliable predictors of counterfeit artesunate in Myanmar were the lack of a Myanmar Reg number and the lack of a hologram on blisterpacks with a manufacturing date after 1998; in Cambodia, the corresponding predictors were low market price and hologram appearance.

This survey suggests that fake artesunate is a substantial public-health problem in southeast Asia. Indeed, it might even be more widespread than our results show, since some shopkeepers hide fakes from unknown buyers, especially in Cambodia where there have been publicity campaigns. Artesunate offers hope to many financially poor countries enduring problems of worsening drug-resistant malaria. However, the spread of these fakes exacerbates an already grim situation. National malaria programmes must monitor the authenticity of antimalarial drugs available through malaria programmes and directly from pharmacies, shops, and the black market. The ingredients for the artesunate testing kit cost the equivalent of about US$0.02 per tablet, compared with about $1.00 for an adult treatment course of artesunate. In the absence of the dye test, examination of the tablets and packaging can be used as surrogate markers of counterfeit artesunate—a simple approach which might be applicable to other counterfeited drugs. However, the characteristics of fakes are likely to change, as the counterfeiters respond and the ingredients of antimalarials must be monitored frequently.

The main difficulty in implementing a programme to verify antimalarial authenticity will be the logistics of testing, especially for the large quantity of artesunate sold over the counter in many small rural shops. Public education on how to detect fakes by their external appearance, as in Cambodia,[2] backed by dye testing and quality assurance, could have a major impact. Prison sentences of 20 years have been given in Vietnam for trading in fake sildenafil,[4] but there have been no prosecutions of fake antimalarial traders. Production is on a large scale; one organisation was delighted to buy 100 000 cheap artesunate tablets, later shown to be counterfeit. The source of these counterfeit tablets is uncertain, but our study suggests that two factories or groups of factories might be involved. The widespread distribution networks of drugs of misuse across porous borders in Asia suggest that the two sources might be linked. Vigorous, coordinated campaigns to monitor drug potency, quality assurance, education, and legal action are needed urgently.

We thank those who collected artesunate samples and helped with the analysis and advice; staff of Médecins sans Frontières-Holland (Myanmar) and Switzerland (Cambodia); the late Dr Singh, Elizabetta Leonardi-Nield, Karela Nitikorn, Mr Billion, Rose McGready, Alan Brockman, Somvang Douangdara, Nitirat Thima, Narangchai Tongyoo, Suwana Techovanich, Ajit Lalvani, and two anonymous contributors. We also thank Guilin Pharmaceuticals, Guilin, China, for their advice. This study was part of the Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.

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Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand (P Newton MRCP, S Proux, K Chotivanich PhD, M Mayxay MD, S Looareesuwan MD, F Nosten MD, N J White FRCP)**; Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Oxford, UK** (P Newton, S Proux, J Farrar MRCP, F Nosten, N J White)**; Shoklo Malaria Research Unit, Mae Sot, Tak Province, Thailand** (S Proux, F Nosten, N J White)**; Division of Parasitic Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA** (M Green MSc)**; Médecins Sans Frontieres (Netherlands), Yangon, Myanmar** (F Smithuis MD)**; Centre for Tropical Diseases, Ho Chi Minh City, Vietnam** (J Farrar)**; European Commission/Cambodia Malaria Control Project, Phnom Penh, Cambodia** (J Rozendaal PhD)**; and Faculty of Pharmacy, Mahidol University, Bangkok, Thailand** (S Prakongpan PhD)

Correspondence to: Prof Nicholas J White, Faculty of Tropical Medicine, Mahidol University, 420/6 Rajvithi Road, Bangkok 10400, Thailand (e-mail: fnnjw@diamond.mahidol.ac.th)

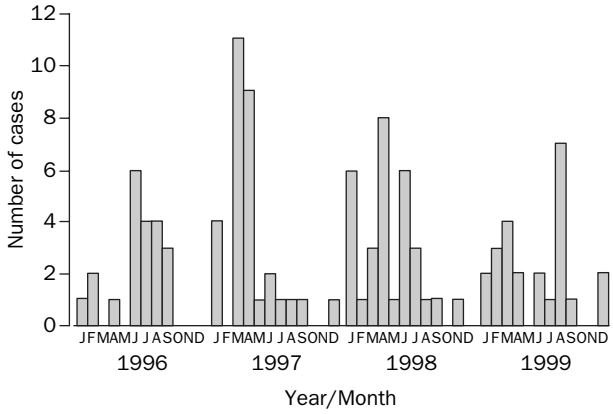
Winter seasonality and rotavirus diarrhoea in adults

Hitoshi Nakajima, Toyoko Nakagomi, Terumi Kamisawa, Nobuhiro Sakaki, Kazunori Muramoto, Takahumi Mikami, Hideyasu Nara, Osamu Nakagomi

We investigated the aetiological role of group A rotavirus in adults with acute diarrhoea in a 4-year prospective study. Of 683 patients with acute diarrhoea, 97 (14%) shed rotavirus as a sole agent, whereas six (5%) of 115 patients without diarrhoea shed rotavirus. Half of patients with rotavirus diarrhoea required admission to hospital. Unlike rotavirus diarrhoea in children, the occurrence of rotavirus-positive cases did not show a significant winter seasonality. Rotavirus infection should be included in the differential diagnosis of diarrhoeal diseases in adults.

Although rotavirus is an important pathogen of severe diarrhoea in infants and young children worldwide, rotavirus infection in adults has had much less attention. Studies in late 1970s and 1980s already showed the presence of symptomatic rotavirus infection in adults, particularly in the elderly;[1–4] what fraction of adult diarrhoea is attributable to rotavirus infection is not known.

Between January, 1996, and December, 1999, we did a 4-year prospective study in which stool samples collected from 683 consecutive patients (both inpatients and outpatients) with acute diarrhoea (mean age 45 years; SD 17 years) in Kuroishi City Hospital in Aomori prefecture (the most Northern prefecture in the main island in Japan) were examined for the presence of group A rotavirus. We used Rotaclone (Meridian Diagnostics, Cincinnati, USA), a commercially-available enzyme-linked immunosorbent assay kit, to test for presence of rotavirus.



Rotavirus-diarrhoea cases by month
The Cosinor method was used to examine the presence of any seasonality. Data were approximated with a cosine curve with a period of 12 months, an amplitude of 1·46 cases (95% CI: 0·73–2·16), and an acrophase (peak) of April 13 (95% CI: March 17 to May 8; p=0·02).

108 (16%) patients shed rotavirus in their stool. Routine bacteriological examination, which we did on all stool samples, showed that pathogenic bacteria (*Vibrio parahaemolyticus* and *Campylobacter jejuni* being the major pathogens) were concurrently isolated from 11 of 108 patients with rotavirus. Thus, rotavirus was the only known pathogen in 14% (97 of 683) of the adult diarrhoea cases, although other viral agents were not sought.

To exclude the possibility that rotavirus was not responsible for the diarrhoeal symptoms, we tested for rotavirus in stool samples obtained from 115 patients who visited the hospital with gastrointestinal diseases other than acute diarrhoea (mostly patients with gastric ulcer or carcinoma). Only six (5%) shed rotavirus in their stool. The odds ratio of rotavirus-positive patients with acute diarrhoea was 2·90 (95% CI 1·24–6·77). Thus, rotavirus infection was the cause of a significantly raised fraction of adult diarrhoea during the 4-year survey period. Unlike rotavirus diarrhoea in infants and young children, which shows a significant winter seasonality, the distribution of rotavirus-positive cases were deviated toward warmer months (figure) and showed a seasonality in which peak incidence occurs in mid-April. The lack of winter seasonality might have contributed to the fact that physicians did not consider rotavirus infection in these patients.

49% (48 of 97) of the rotavirus-positive samples were from patients admitted to hospital with acute diarrhoea. This high proportion of hospital admissions might be due in part to the fact that this hospital serves as the referral hospital in a broader rural area of Southern Tsugaru region where the total population is about 100 000. Severe dehydrating rotavirus diarrhoea has been infrequently reported in adults[1,2] and was previously reported in Japan in 1994.[5] Identification of viral agents, even in cases in which pathogenic bacteria are not identified, is not part of the general practice in Japan. The average age of patients who were admitted to hospital with rotavirus diarrhoea was 50 (SD 21 years), older than the average age (39 years; SD 15 years) of patients with rotavirus treated only at the outpatient department (t-test, p=0·002).

We have shown the importance of identifying rotavirus in the elderly, but severe rotavirus infection requiring admission to hospital is not restricted to the elderly. Physicians should include rotavirus infection in the differential diagnosis of diarrhoeal diseases in adults, regardless of age or the season.

We thank Drs Y Motohashi and K Murata for their assistance in statistical analysis.

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Department of Medicine, Tokyo Metropolitan Komagome Hospital, Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan (H Nakajima MD, T Kamisawa MD, N Sakaki MD)**; Department of Medicine, Kuroishi City Hospital, Kuroishi 036-0541, Japan** (K Muramoto MD, T Mikami MD, H Nara MD)**; and Department of Microbiology, Akita University School of Medicine, Hondo, Akita 010-8543, Japan** (T Nakagomi MD, Prof O Nakagomi MD)

Correspondence to: Prof O Nakagomi (e-mail: onakagom@ipc.akita-u.ac.jp)