pressure may reveal upper airway collapsibility. This is especially useful for detecting obstructive sleep apnoea syndrome in obese snorers [4, 10]. Thus, in the present case, the NEP technique would have allowed the recognition of extrathoracic EFL, which may have contributed to our patient's hypoxaemia. However, when this phenomenon extends to the whole expiration during NEP, it may preclude the detection of intrathoracic EFL with this method [10]. Actually, it is unlikely that upper airway collapse may account for the acute cardiorespiratory disaster experienced by our patient. The patient was awake, he was moved and positive pressure NIV was continuously applied with 8 cmH_2O PEEP during this period. Finally, a growing body of evidence suggests that the deterioration of pulmonary gas exchange that occurs when obese patients are lying down may be the result of ventilation/perfusion mismatch rather than a consequence of hypoventilation [7, 8]. When morbidly obese patients are lying down, their small airways may extensively collapse in the posterior dependent lung zones. These nonaerated pulmonary areas are well perfused in the supine position and may rapidly lead to severe refractory hypoxaemia [8].

To summarise, it is noteworthy that the sitting position not only ensures comfort but may also be part of a strategy preventing severe cardiorespiratory complications in superobese patients.

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REFERENCES

1 Finucane MM, Stevens GA, Cowan MJ, *et al.* National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet* 2011; 377: 557–567.
2 Tsueda K, Debrand M, Zeok SS, *et al.* Obesity supine death syndrome: reports of two morbidly obese patients. *Anesth Analg* 1979; 58: 345–347.
3 Ninane V, Leduc D, Kafi SA, *et al.* Detection of expiratory flow limitation by manual compression of the abdominal wall. *Am J Respir Crit Care Med* 2001; 163: 1326–1330.
4 Ferretti A, Giampiccolo P, Cavalli A, *et al.* Expiratory flow limitation and orthopnea in massively obese subjects. *Chest* 2001; 119: 1401–1408.
5 Pankow W, Podszus T, Gutheil T, *et al.* Expiratory flow limitation and intrinsic positive end-expiratory pressure in obesity. *J Appl Physiol* 1998; 85: 1236–1243.
6 Steier J, Jolley CJ, Seymour J, *et al.* Neural respiratory drive in obesity. *Thorax* 2009; 64: 719–725.
7 Yamane T, Date T, Tokuda M, *et al.* Hypoxemia in inferior pulmonary veins in supine position is dependent on obesity. *Am J Respir Crit Care Med* 2008; 178: 295–299.
8 Pelosi P, Croci M, Ravagnan I, *et al.* Respiratory system mechanics in sedated, paralyzed, morbidly obese patients. *J Appl Physiol* 1997; 82: 811–818.
9 Pepe PE, Marini JJ. Occult positive end-expiratory pressure in mechanically ventilated patients with airflow obstruction: the auto-PEEP effect. *Am Rev Respir Dis* 1982; 126: 166–170.
10 Verin E, Tardif C, Portier F, *et al.* Evidence for expiratory flow limitation of extrathoracic origin in patients with obstructive sleep apnoea. *Thorax* 2002; 57: 423–428.

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High initial multidrug-resistant tuberculosis rate in Buenaventura, Colombia: a public–private initiative

To the Editors:

Multidrug-resistant tuberculosis (MDR-TB) is defined as TB resistant to at least isoniazid and rifampicin and globally accounts for approximately 500,000 new cases and 150,000 deaths each year [1]. In the latest nationwide anti-TB drug resistance survey carried out in Colombia (2005), MDR-TB accounted for 2.4% of new cases (initial MDR-TB) and 31.4% of previously treated cases [2]. Colombia has 32 departments, 11,000 TB cases per year and three laboratories to perform drug susceptibility testing (DST). Valle del Cauca is the third most populated department and the one with the highest TB caseloads in Colombia, where previous studies had reported 6% of initial MDR-TB [3], suggesting that the problem may be greater than in the rest of the country.

A public–private initiative (PPI) led by the Secretariat of Public Health (SPH) of Valle del Cauca and the Centro Internacional de Entrenamiento e Investigaciones Médicas (CIDEIM) was established to assess the anti-TB drug-resistance situation in this department between January 2007 and December 2008, through operational research. The cities were weighted based on elevated rates of TB: Cali and Buenaventura, which represent 70% of the total caseload in the department (1,700 cases per year). This study was approved by the Ethics Committee of CIDEIM.

Included cases were the following: smear-positive pulmonary TB, previously-untreated and/or previously-treated (including relapse, reinfection and treatment failures or defaulters), residing in the city during the last 12 months, regardless of age. Both

public and private health facilities in Cali and Buenaventura were invited to submit fresh sputum samples or isolates of acid-fast bacilli of these cases. In Cali, the local TB programme gave priority to patients less than 16 yrs of age and those from public primary health facilities. In Buenaventura, priority was given to all new cases with positive cultures also from public primary health facilities. 11 other smaller cities were also included; only previously treated cases from public health facilities were sampled. For all patients, TB medication history was obtained from their TB treatment cards. DSTs were performed in the BSL-III laboratory of CIDEIM, using the agar proportion method [4] with Middlebrook 7H10 medium with the following first-line drug (FLD) concentrations: isoniazid (INH) 0.2 and 1.0 $\mu g \cdot mL^{-1}$, rifampicin (RMP) 1.0 $\mu g \cdot mL^{-1}$, streptomycin (SM) 2.0 $\mu g \cdot mL^{-1}$ and ethambutol (EMB) 5.0 $\mu g \cdot mL^{-1}$. Pyrazinamide (PZA) resistance was determined by pyrazinamidase assay. External quality control was performed by the Mycobacteriology Laboratory of National Jewish Health (Denver, Colorado, USA) with concordance of 100% for INH, RMP and SM; 83% for PZA and 54% for EMB. MDR isolates were genotyped using spoligotyping [5]. The spoligopatterns obtained were independently analysed by two readers and compared with the SITVIT2 database (Pasteur Institute of Guadeloupe, Les Abymes, Guadeloupe, France). Statistical analysis was conducted with Stata version 9.0 (StataCorp LP, College Station, TX, USA), Chi-squared and Fisher's exact tests were used to determine differences with 5% significance level. A confidence interval of 95% was calculated to proportions.

During this PPI, 299 patients with culture-positive pulmonary TB were included, of which 259 (87%) were from public health facilities. The median age was 34 yrs (range 4–97 yrs), 179 (60.0%) of patients were male. Eight (2.7%) cases were less than 16 yrs of age. Of the 299 TB patients, 182 (60.8%) were new TB cases, the remaining 117 (39.2%) were previously treated cases. Approximately half of the cases (n=142) were from Buenaventura. In this city, 97% of the cases came from public health facilities, of which, 75% belonged to primary level of care.

The patterns of resistance to the different drugs for all previously-untreated and -treated cases are presented in table 1. Of the strains isolated from the 182 new TB cases, 53 (29.1%) were resistant to any FLD, whereas 76 (65%) of the previously-treated cases had resistance to any drug. Among new TB cases, 8.2% (CI 95% 4–12%) were monoresistant to INH. Of those, three isolates were resistant at 0.2 $\mu g \cdot mL^{-1}$ but susceptible at 1.0 $\mu g \cdot mL^{-1}$ (two cases from Buenaventura and one from Cali). This INH-concentration-related resistance pattern was also found in two treated cases: one monoresistant and one MDR-TB from Buenaventura. The overall resistance to INH was 24.7% (95% CI 17–19), of which 40% were MDR strains. Initial MDR-TB accounted for 9.9% (95% CI 6–14), with Buenaventura alone accounting for 9.1% (95% CI 4.8–15). Seven of the 18 primary MDR-TB cases were resistant to all FLDs. Approximately half (47%) of the previously treated cases were MDR-TB (95% CI 45–63) and this pattern represented around a quarter of all the isolates (24.4%).

From the total of 73 MDR-TB isolates, DNA could be extracted from 68 (93.1%). 10 genotypes could be identified: LAM9, Beijing, H1, U, LAM3, LAM2, X1, S, T2-Uganda, LAM5. Beijing family strain (spoligotype international type (SIT) 190) represented a

TABLE 1 Drug-resistance patterns of *Mycobacterium tuberculosis* among new and previously treated patients from Valle del Cauca, Colombia in 2007–2008

	Buenaventura[#]		Cali[¶]		Other cities		Total Valle del Cauca[+]			
	PU	PT	PU	PT	PT	PU	PT	Total cases	p-value[§]
Total n/N (%)	142/182 (78.0)	54/117 (46.2)	40/182 (22)	39/117 (33.3)	24/117 (20.5)	182/299 (60.9)	117/299 (39.1)	299 (100)	
Susceptible to INH+RMP+SM+EMB	96 (67.6)	16 (29.6)	28 (70)	17 (43.5)	7 (29.2)	124 (68.1)	40 (34.1)	164 (54.8)	<0.001
Resistance to any drug[/]	46 (32.4)	38 (70.4)	12 (30)	22 (56.4)	17 (70.8)	53[§§] (29.1)	76 (65)	129 (43.1)	<0.001
Any resistance to INH[#,##]	32/142 (22.5)	38/54 (70.4)	9/40 (22.5)	18/39 (46.1)	14/24 (58.3)	41/182 (22.5)	70/117 (59.8)	111/299 (37.1)	<0.001
Monoresistance to INH	12 (8.4)	6 (11.1)	3 (7.5)	1 (2.6)	3 (12.5)	15 (8.2)	10 (8.5)	25 (8.4)	0.94
Monoresistance to SM[¶,¶]	9 (6.3)	0	2 (5)	1 (2.6)	1 (4.2)	11 (6.0)	2 (1.7)	13 (4.3)	0.06
Monoresistance to RMP	0	0	0	1 (2.6)	0	0	1 (0.9)[/]	1 (0.3)	
Resistance to INH+SM	7 (4.9)	2 (3.7)	1 (2.5)	3 (7.7)	0	8 (4.4)	5 (4.3)	13 (4.3)	0.94
Resistance to INH+RMP	3 (2.1)	3 (5.6)	3 (7.5)	1 (2.6)	3 (12.5)	6 (3.3)	7 (6.0)	13 (4.3)	0.26
Resistance to INH+RMP+SM	3 (2.1)	9 (16.7)	1 (2.5)	7 (17.9)	5 (20.8)	4 (2.2)	21 (17.9)	25 (8.4)	<0.001
Resistance to INH+RMP+SM+EMB	7 (4.9)	18 (33.3)	1 (2.5)	6 (15.4)	3 (12.5)	8 (4.4)	27 (23.1)	35 (11.7)	<0.001
Multi-drug resistance/MDR[++]	13 (9.1)[#,##]	30 (55.6)	5 (12.5)[¶,¶,¶]	14 (35.9)	11 (45.8)	18 (9.9)	55 (47.0)	73 (24.4)	<0.001

Data are presented as n (%), unless otherwise stated. PU: previously-untreated cases (*i.e.* new tuberculosis cases); PT: previously-treated cases (including relapse, reinfection, and treatment failures or defaulters); INH: isoniazid; RMP: rifampicin; SM: streptomycin; EMB: ethambutol; PZA: pyrazinamide. The most important combinations are shown. [#]: n=196; [¶]: n=79; [+]: n=299; [§]: Chi-squared (PU *versus* PT); [/]: resistant to INH or RMP or EMB or SM or PZA; [#,#]: five strains were resistant for INH at 0.2 $\mu g \cdot mL^{-1}$ and susceptible at 1.0 $\mu g \cdot mL^{-1}$ see text for more details; [¶,¶]: one PU missing datum for Cali and Buenaventura; [++]: resistance to at least both INH and RMP; [§§]: five missing data because no data available for EMB; [/,/]: confirmed (HIV-infected patient), monoresistance to EMB or PZA was zero; [#,#]: one case was less than 16 yrs of age; [¶,¶,¶]: two cases were less than 16 yrs of age.

cluster of 22 cases (20 from Buenaventura) and orphan genotypes accounted for four isolates. The genotype H1 was identified only among previously-treated cases. There was no statistically significant difference between isolates from previously untreated and previously treated cases (Fisher's exact test p=0.15). There was a high frequency of Beijing strains among MDR-TB isolates. Eight of 20 Beijing strains were involved in a cluster of new cases, suggesting recent ongoing transmission.

In this study, the resistance patterns for new TB cases revealed that 40% of INH-resistant isolates were also RMP-resistant and the remaining isolates were at risk for further amplification of drug-resistance given the monotherapy with RMP during the continuation phase of the standard regimen [6]. The rate (9.1%) of initial MDR-TB found in Buenaventura is the highest reported in Colombia. This operational research study used a convenience sample. In Cali, the sample accounted for only 3.5% of the total number of new TB cases in that period and the MDR-TB proportion could have been overestimated. However, in Buenaventura this sample accounted for 28.2% of new TB cases, and these do not necessarily have risk factors other than residing in this very high TB burden setting.

Public–private mix for TB care and control is among the core components of the STOP TB Strategy [7]. Most of these experiences have focused on engagement with the programmatic management of drug-resistant TB and with advocacy, communication and social mobilisation activities [8].

Based on this initiative, the SPH of Valle del Cauca and the public reference hospital of the region established a ''Drug-Resistant (DR)-TB Committee'' to recommend the proper management for such cases (from both public and private health facilities), which was a significant achievement, given that Colombia does not have universal access to healthcare. To our knowledge, this is the first report of a PPI focusing on case finding of DR-TB in Latin-America. We detected primary MDR-TB cases which otherwise would not have been found, thereby having significant impact on TB control and treatment outcome. Furthermore, national tuberculosis programmes in many high-TB-burden countries do not have the resources for detecting and treating MDR-TB patients as in Colombia, so public–private mix strategies could be efficient ways to build human and laboratory capacity.

In summary, the rate of initial MDR-TB may be greater than 6% in Buenaventura. This city has the highest incidence rate of TB in Colombia (72 cases per 100,000 population in 2008) and high rates of default (9–14% in 2007–2008) and of transmission of MDR-TB Beijing strains. Therefore, it is imperative to reduce default rates and to increase cure rates of both drug-susceptible and drug-resistant TB cases, through the following strategies: 1) building laboratory capacity for performing DST to both FLDs and second-line drugs (SLDs) (including rapid molecular testing for the detection INH- and RMP-resistance); 2) securing uninterrupted access to both FLDs and SLDs; and 3) assuring appropriate medical follow-up for the early detection of treatment failure and for ascertaining definitive cure. ''Engaging all healthcare providers'' could be an efficient TB control strategy to overcome these challenges.

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REFERENCES

1 World Health Organization. Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response. 2010; WHO/HTM/TB/2010.3: 1–3.

2 Garzon MC, Angee DY, Llerena C, *et al.* Surveillance of *Mycobacterium tuberculosis* resistance to antituberculosis drugs. *Biomédica* 2008; 28: 319–326.

3 Moreira CA, Hernandez HL, Arias NL, *et al.* Initial drug resistance as a threat for tuberculosis control: the case of Buenaventura, Colombia. *Biomédica* 2004; 24: Suppl. 1, 73–79.

4 World Health Organization. Policy guidance on drug-susceptibility testing (DST) of second-line antituberculosis drugs. Geneva, WHO Press, 2008.WHO/HTM/TB/2008.392; available from http://whqlibdoc.who.int/hq/2008/WHO_HTM_TB_2008.392_eng.pdf Date last updated: 2008; Date last accessed: April 23, 2012.

5 Kamerbeek J, Schouls L, Kolk A, *et al.* Simultaneous detection and strain differentiation of *Mycobacterium tuberculosis* for diagnosis and epidemiology. *J Clin Microbiol* 1997; 35: 907–914.

6 Caminero JA. Likelihood of generating MDR-TB and XDR-TB under adequate National Tuberculosis Control Programme implementation. *Int J Tuberc Lung Dis* 2008; 12: 869–877.
7 World Health Organization. Public-Private Mix for TB Care and Control A toolkit. Geneva, WHO, 2010. WHO/HTM/TB/2010.12; available from www.who.int/tb/careproviders/ppm/PPMToolkit.pdf Date last updated: 2012; Date last accessed: February 8, 2012.
8 Malmborg R, Mann G, Squire SB. A systematic assessment of the concept and practice of public-private mix for tuberculosis care and control. *Int J Equity Health* 2011; 10: 49.

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No associations of the mineralocorticoid and glucocorticoid receptor genes with asthma

To the Editors:

Asthma is a multifactorial disease. Although a number of host and environmental risk factors have been identified in the past decades, these cannot fully explain the prevalence of asthma. Previous studies have shown that psychosocial stress confers a risk for the development of asthma [1].

Stress activates the hypothalamus–pituitary–adrenal (HPA) axis, which leads to secretion of cortisol. Cortisol in turn influences the activity of many systems in the human body and shifts, among others, the T-helper type (Th1/Th2) balance of the peripheral blood mononuclear cells towards a predominantly type 2 response. Cortisol binds to the high affinity mineralocorticoid receptor (*NR3C2*) and the low affinity glucocorticoid receptor (*NR3C1*). Single nucleotide polymorphisms (SNPs) in these receptors have been associated with basal cortisol and cortisol responses to stress [2]. So far, two studies have found an association between SNPs in *NR3C1* (*i.e.* rs6195, rs41423247) and asthma development [3, 4]. However, these results have not been replicated in other populations so far. Additionally, it is unknown whether other functional or tagging SNPs in the *NR3C1* are associated with asthma development. In addition, SNPs in the *NR3C2* have not been studied before in relation to asthma development. Also it is yet unclear whether exposure to psychosocial stress modifies the effect of SNPs in *NR3C2* or *NR3C1* on asthma.

We investigated the associations of SNPs in *NR3C2* or *NR3C1* with asthma in adolescents from the general population and attempted to replicate our findings in an asthma case–control study.

In adolescents from the general population, we have previously shown that exposure to perinatal stress more than doubles the risk of asthma development [5]. Therefore, we tested additionally whether exposure to perinatal stress modifies the effect of SNPs in *NR3C2* or *NR3C1* on asthma in adolescents.

We genotyped two functional SNPs in *NR3C2* (rs5522, rs2070951) and 12 functional or tagging SNPs in *NR3C1* (rs4912903, rs6198, rs6196, rs258813, rs33388, rs17100236, rs10482642, rs2963155, rs41423247, rs9324924, rs4244032, rs4607376) in 1,454 adolescents of the prospective TRacking Adolescents' Individual Lives Survey (TRAILS) cohort (48% males; mean $\pm$SD age at survey 1, 11 $\pm$ 0.6 yrs; survey 2, 14 $\pm$ 0.5 yrs; survey 3, 16 $\pm$ 0.7 yrs) [6] and in 998 individuals from the Dutch Asthma GWAS study (44% males; mean $\pm$SD age 42 $\pm$ 12.2 yrs) [7], that acted as replication study. In TRAILS, data on parentally reported asthma was collected at age 11, 14 and 16 yrs *via* self-reported questionnaires [8]. Asthma was defined as a doctor diagnosis of asthma, and/or symptoms of asthma and/or asthma treatment prescribed by a physician in the past 12 months, before or at the age of 16 years (n=141; 10%). Adolescents not meeting these criteria were defined as not having asthma (n=1,293; 89%). Information about asthma was missing in 20 adolescents (1%). The replication study consisted of 529 asthmatics and 469 nonasthmatics; asthma was defined as a doctor's diagnosis of asthma, the presence of asthma symptoms and bronchial hyperresponsiveness [7]. In TRAILS, perinatal stress was defined as *in utero* exposure to the mother's self-reported maternal psychological problems and/or self-reported maternal postnatal depression (n=67 adolescents; 5%) [9].

SNPs were analysed in an additive genetic model for the effect on asthma using logistic regression models. Interactions between genotype and perinatal stress were tested in TRAILS by introduction of perinatal stress and the interaction term of genotype times perinatal stress into the model.

None of the SNPs in *NR3C2* or *NR3C1* were significantly associated with asthma in adolescents. We also found no association between these SNPs in *NR3C2* or *NR3C1* and asthma in the replication study (table 1).

We observed no effect of perinatal stress on the association between SNPs in *NR3C2* or *NR3C1* and asthma in adolescents (*i.e.* no interaction between perinatal stress and SNPs).

Previous studies have shown that SNPs in *NR3C1* (*i.e.* rs6195, rs41423247) were associated with asthma [3, 4]. Our results do not support the findings of these previous studies, specifically not those suggesting that a mutation (G/C) within rs41423247 in *NR3C1* would have a protective effect on asthma development [4]. However, this association was shown in merely one study including only 59 adults with asthma and 70 healthy adults. Since we found neither an association between rs41423247 and asthma in 1,434 adolescents (OR 0.99, 95% CI 0.76–1.28) nor in 998 adult individuals (OR 0.96, 95% CI 0.80–1.15), we feel that the findings from the study of PIETRAS *et al*. [4] may be due to chance.

Although we found no association between SNPs in the glucocorticoid or mineralocorticoid receptor and asthma, this does not exclude a role of glucocorticoid or mineralocorticoid receptor activity in asthma development, since this activity is