## Universal health coverage in Turkey: enhancement of equity

*Atun R. et al.*

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Turkey has successfully introduced health system changes and provided its citizens with the right to health to achieve universal health coverage, which helped to address inequities in financing, health service access, and health outcomes. We trace the trajectory of health system reforms in Turkey, with a particular emphasis on 2003—13, which coincides with the Health Transformation Program (HTP). The HTP rapidly expanded health insurance coverage and access to health-care services for all citizens, especially the poorest population groups, to achieve universal health coverage. We analyse the contextual drivers that shaped the transformations in the health system, explore the design and implementation of the HTP, identify the factors that enabled its success, and investigate its effects. Our findings suggest that the HTP was instrumental in achieving universal health coverage to enhance equity substantially, and led to quantifiable and beneficial effects on all health system goals, with an improved level and distribution of health, greater fairness in financing with better financial protection, and notably increased user satisfaction. After the HTP, five health insurance schemes were consolidated to create a unified General Health Insurance scheme with harmonised and expanded benefits. Insurance coverage for the poorest population groups in Turkey increased from 2•4 million people in 2003, to 10•2 million in 2011. Health service access increased across the country—in particular, access and use of key maternal and child health services improved to help to greatly reduce the maternal mortality ratio, and under-5, infant, and neonatal mortality, especially in socioeconomically disadvantaged groups. Several factors helped to achieve universal health coverage and improve outcomes. These factors include economic growth, political stability, a comprehensive transformation strategy led by a transformation team, rapid policy translation, flexible implementation with continuous learning, and simultaneous improvements in the health system, on both the demand side (increased health insurance coverage, expanded benefits, and reduced cost-sharing) and the supply side (expansion of infrastructure, health human resources, and health services).

## New evidence about an old drug — Risk with codeine after adenotonsillectomy

*Racoosin J.A., et al.*

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During the past 10 years, efforts in pharmacogenomics have generated insights into the efficacy and safety of drugs, enhancing our understanding of the safety profile of even some of the oldest drugs, such as codeine sulfate, an opioid analgesic first approved in 1950 for relief of mild or moderate pain in patients after adenotonsillectomy.

The activity of codeine depends on its conversion to morphine by the cytochrome P-450 isoenzyme 2D6 (CYP2D6); morphine is subsequently metabolized to the active morphine-6-glucuronide by means of UDP-glucuronosyltransferase 2B7. The gene encoding CYP2D6 has many genetic variations that affect the amount of codeine that is converted to an active form and that result in the drug's variable effect. Patients with a normal range of CYP2D6 activity represent 75 to 92% of the population and are called extensive metabolizers. At the low end of the activity spectrum are poor metabolizers (approximately 5 to 10% of the population), who have no functional alleles and therefore receive little to no morphine or analgesia from codeine. At the high end of the CYP2D6 activity spectrum, ultrarapid metabolizers have two or more functional alleles, and their bodies can convert codeine into large amounts of morphine. The prevalence of ultrarapid metabolism varies by ethnic group: it is lower

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than 1% among Chinese and Japanese patients but potentially higher than 15% among Middle Eastern and North African patients. Clinically significant toxic effects related to opioid excess have been reported in ultrarapid metabolizers, which suggests that the risk of toxic effects from codeine depends, in part, on genotype.

In April 2012, a case series was published reporting two deaths and one case of respiratory depression in children 3 to 5 years of age who had received typical doses of codeine after tonsillectomy, adenoidectomy, or both performed because of obstructive sleep apnea. The two deaths occurred in children who had evidence of being ultrarapid metabolizers, and the postmortem morphine levels in these children were substantially higher than the therapeutic range. The third child was an extensive metabolizer. Signs of morphine toxicity developed in that patient within 1 to 2 days after codeine treatment began.

## Racemic adrenaline and inhalation strategies in acute bronchiolitis

*Håvard Ove Skjerven, et al.*

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Acute bronchiolitis in infants frequently results in hospitalization, but there is no established consensus on inhalation therapy — either the type of medication or the frequency of administration — that may be of value. Assessment of the effectiveness of inhaled racemic adrenaline as compared with inhaled saline and the strategy for frequency of inhalation (on demand vs. fixed schedule) in infants hospitalized with acute bronchiolitis was studied.

In the eight-center, randomized, double-blind trial with a 2-by-2 factorial design, compared inhaled racemic adrenaline with inhaled saline and on-demand inhalation with fixed-schedule inhalation (up to every 2 hours) in infants (<12 months of age) with moderate-to-severe acute bronchiolitis. An overall clinical score of 4 or higher (on a scale of 0 to 10, with higher scores indicating more severe illness) was required for study inclusion. Any use of oxygen therapy, nasogastric-tube feeding, or ventilatory support was recorded. The primary outcome was the length of the hospital stay, with analyses conducted according to the intention-to-treat principle.

The mean age of the 404 infants included in the study was 4.2 months, and 59.4% were boys. Length of stay, use of oxygen supplementation, nasogastric-tube feeding, ventilatory support, and relative improvement in the clinical score from baseline (preinhalation) were similar in the infants treated with inhaled racemic adrenaline and those treated with inhaled saline (P>0.1 for all comparisons). On-demand inhalation, as compared with fixed-schedule inhalation, was associated with a significantly shorter estimated mean length of stay — (P=0.01) — as well as less use of oxygen supplementation (P=0.04), less use of ventilatory support (P=0.01), and fewer inhalation treatments (P<0.001).

In the treatment of acute bronchiolitis in infants, inhaled racemic adrenaline is not more effective than inhaled saline.

## Targeted versus universal decolonization to prevent ICU infection

*Susan S. Huang, et al.*

*N Engl J Med 2013; 368:2255-2265*

Both targeted decolonization and universal decolonization of patients in intensive care units (ICUs) are candidate strategies to prevent health care–associated infections, particularly those caused by methicillin-resistant Staphylococcus aureus (MRSA).

Hospitals were randomly assigned to one of three strategies, with all adult ICUs in a given hospital assigned to the same strategy. Group 1 implemented MRSA screening and isolation; group 2, targeted decolonization (i.e., screening, isolation, and decolonization of MRSA carriers); and group 3, universal decolonization (i.e., no screening, and decolonization of all patients). Proportional-hazards models were used to assess differences in infection reductions across the study groups, with clustering according to hospital.

Universal decolonization resulted in a significantly greater reduction in the rate of all bloodstream infections than either targeted decolonization or screening and isolation. One bloodstream infection was prevented per 54 patients who underwent decolonization. The reductions in rates of MRSA bloodstream infection were similar to those of all bloodstream infections, but the difference was not significant. Adverse events, which occurred in 7 patients, were mild and related to chlorhexidine.

In routine ICU practice, universal decolonization was more effective than targeted decolonization or screening and isolation in reducing rates of MRSA clinical isolates and bloodstream infection from any pathogen.

## Urinary-cell mRNA profile and acute cellular rejection in kidney allografts

*Manikkam Suthanthiran, et al.*

*N Engl J Med 2013; 369:20-31*

Although the standard test for the diagnosis of acute rejection in kidney transplants is the renal biopsy, noninvasive tests would be preferable.

4300 urine specimens prospectively collected from 485 kidney-graft recipients from day 3 through month 12 after transplantation. Messenger RNA (mRNA) levels were measured in urinary cells and correlated with allograft-rejection status with the use of logistic regression.

A three-gene signature of 18S ribosomal (rRNA)–normalized measures of CD3 mRNA and interferon-inducible protein 10 (IP-10) mRNA, and 18S rRNA discriminated between biopsy specimens showing acute cellular rejection and those not showing rejection (area under the curve [AUC], 0.85; 95% confidence interval [CI], 0.78 to 0.91; P<0.001 by receiver-operating-characteristic curve analysis). The cross-validation estimate of the AUC was 0.83 by bootstrap resampling, and the Hosmer–Lemeshow test indicated good fit (P=0.77). In an external-validation data set, the AUC was 0.74 (95% CI, 0.61 to 0.86; P<0.001) and did not differ significantly from the AUC in our primary data set (P=0.13). The signature distinguished acute cellular rejection from acute antibody-mediated rejection and borderline rejection (AUC, 0.78; 95% CI, 0.68 to 0.89; P<0.001). It also distinguished patients who received anti–interleukin-2 receptor antibodies from those who received T-cell–depleting antibodies (P<0.001) and was diagnostic of acute cellular rejection in both groups. Urinary tract infection did not affect the signature (P=0.69). The average trajectory of the signature in repeated urine samples remained below the diagnostic threshold for acute cellular rejection in the group of patients with no rejection, but in the group with rejection, there was a sharp rise during the weeks before the biopsy showing rejection (P<0.001).

A molecular signature of CD3 mRNA, IP-10 mRNA, and 18S rRNA levels in urinary cells appears to be diagnostic and prognostic of acute cellular rejection in kidney allografts.

## A congenital neutrophil defect syndrome associated with mutations in VPS45

*Thierry Vilboux, et al.*

*N Engl J Med 2013; 369:54-6*

Neutrophils are the predominant phagocytes that provide protection against bacterial and fungal infections. Genetically determined neutrophil disorders confer a predisposition to severe infections and reveal novel mechanisms that control vesicular trafficking, hematopoiesis, and innate immunity.

We clinically evaluated seven children from five families who had neutropenia, neutrophil dysfunction, bone marrow fibrosis, and nephromegaly. To identify the causative gene, we performed homozygosity mapping using single-nucleotide polymorphism arrays, whole-exome sequencing, immunoblotting, immunofluorescence, electron microscopy, a real-time quantitative polymerase–chain-reaction assay, immunohistochemistry, flow cytometry, fibroblast motility assays,

measurements of apoptosis, and zebrafish models. Correction experiments were performed by transfecting mutant fibroblasts with the nonmutated gene.

All seven affected children had homozygous mutations (Thr224Asn or Glu238Lys, depending on the child's ethnic origin) in VPS45, which encodes a protein that regulates membrane trafficking through the endosomal system. The level of VPS45 protein was reduced, as were the VPS45 binding partners rabenosyn-5 and syntaxin-16. The level of β1 integrin was reduced on the surface of VPS45-deficient neutrophils and fibroblasts. VPS45-deficient fibroblasts were characterized by impaired motility and increased apoptosis. A zebrafish model of vps45 deficiency showed a marked paucity of myeloperoxidase-positive cells (i.e., neutrophils). Transfection of patient cells with nonmutatedVPS45 corrected the migration defect and decreased apoptosis.

Defective endosomal intracellular protein trafficking due to biallelic mutations in VPS45 underlies a new immunodeficiency syndrome involving impaired neutrophil function.

## Effect of provision of daily zinc and iron with several micronutrients on growth and morbidity among young children in Pakistan: a cluster-randomised trial

*S. Soofi et al.,*

*Lancet 2013; 368*

Powders containing iron and other micronutrients are recommended as a strategy to prevent nutritional anaemia and other micronutrient deficiencies in children. The effects of provision of two micronutrient powder formulations, with or without zinc, to children in Pakistan were assessed in this study.

A baseline survey identified 256 clusters, which were randomly assigned (within urban and rural strata, by computer-generated random numbers) to one of three groups: non-supplemented control (group A), micronutrient powder without zinc (group B), or micronutrient powder with 10 mg zinc (group C). Daily to 18 months of age follow-up was to age 2 years. Micronutrient powder sachets for groups B and C were identical except for colour. Parents knew whether their child was receiving supplementation, but did not know whether the powder contained zinc. Primary outcomes were growth, episodes of diarrhoea, acute lower respiratory tract infection, fever, and incidence of admission to hospital.

947 children were enrolled in group A clusters, 910 in group B clusters, and 889 in group C clusters. Micronutrient powder administration was associated with lower risk of iron-deficiency anaemia at 18 months compared with the control group (without zinc=0.20; OR for micronutrient powder with zinc=0•25). Compared with the control group, children in the group receiving micronutrient powder without zinc gained an extra 0•31 cm between 6 and 18 months of age and children receiving micronutrient powder with zinc an extra 0•56 cm. But, strong evidence of an increased proportion of days with diarrhoea (p=0•001) and increased incidence of bloody diarrhoea (p=0•003) between 6 and 18 months in the two micronutrient powder groups, and reported chest indrawing (p=0•03) should be taken into consideration. Incidence of febrile episodes or admission to hospital for diarrhoea, respiratory problems, or febrile episodes did not differ between the three groups.

Use of micronutrient powders reduces iron-deficiency anaemia in young children. However, the excess burden of diarrhoea and respiratory morbidities associated with micronutrient powder.

## Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk

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Recent studies in animals have shown a mechanistic link between intestinal microbial metabolism of the choline moiety in dietary phosphatidylcholine (lecithin) and coronary artery disease through the production of a

proatherosclerotic metabolite, trimethylamine-N-oxide (TMAO). In this study the relationship among intestinal microbiota-dependent metabolism of dietary phosphatidylcholine, TMAO levels, and adverse cardiovascular events in humans are evaluated.

Plasma and urinary levels of TMAO and plasma choline and betaine levels were quantified by means of liquid chromatography and online tandem mass spectrometry after a phosphatidylcholine challenge (ingestion of two hard-boiled eggs and deuterium [d9]-labeled phosphatidylcholine) in healthy participants before and after the suppression of intestinal microbiota with oral broad-spectrum antibiotics. The relationship between fasting plasma levels of TMAO and incident major adverse cardiovascular events (death, myocardial infarction, or stroke) during 3 years of follow-up were further examined in 4007 patients undergoing elective coronary angiography.

Time-dependent increases in levels of both TMAO and its d9 isotopologue, as well as other choline metabolites, were detected after the phosphatidylcholine challenge. Plasma levels of TMAO were markedly suppressed after the administration of antibiotics and then reappeared after withdrawal of antibiotics. Increased plasma levels of TMAO were associated with an increased risk of a major adverse cardiovascular event (hazard ratio for highest vs. lowest TMAO quartile, 2.54; 95% confidence interval, 1.96 to 3.28; $P<0.001$). An elevated TMAO level predicted an increased risk of major adverse cardiovascular events after adjustment for traditional risk factors ($P<0.001$), as well as in lower-risk subgroups.

The production of TMAO from dietary phosphatidylcholine is dependent on metabolism by the intestinal microbiota. Increased TMAO levels are associated with an increased risk of incident major adverse cardiovascular events.