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shock. There is little opportunity for pretreatment in this setting and there is invariably a delay to optimum platelet inhibition with even the most effective oral agents.<sup>14</sup> A randomised trial of cangrelor versus placebo on top of optimum dual oral antiplatelet therapy, including either ticagrelor or prasugrel, would help solidify its role in this setting. Second, because patients with high-risk non-STEMI (GRACE score >140) preferentially benefit from early intervention,<sup>15</sup> cangrelor, with its rapid onset and offset, might offer an advantage in this population. Third, in centres where pretreatment is not routine clinical practice, cangrelor will probably become a preferred option. Fourth, cangrelor is an attractive option in patients with high-risk anatomic or clinical features undergoing same-sitting or ad hoc elective PCI for stable coronary artery disease. There is little opportunity to benefit from preloading in these patients and, somewhat surprisingly, neither ticagrelor nor prasugrel has been formally studied in this large group of patients.

Finally, will cangrelor offer value for money? The cost differential between the intravenous infusion of cangrelor and a loading dose of an oral antiplatelet drug (ticagrelor, prasugrel, or clopidogrel) is likely to be substantial. Moreover, the degree to which the reduction in ischaemic events makes cangrelor an overall cost-effective strategy will be a major determinant of how widely it is used. Despite these considerations, its favourable pharmacodynamic profile and effectiveness in reducing periprocedural events makes cangrelor a useful and welcome agent for interventional cardiologists and their patients.

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- 1 Go AS, Mozaffarian D, Roger VL, et al, for the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation* 2013; **127**: e6–e245.
- 2 Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003; **361**: 13–20.
- 3 Mehta SR, Cannon CP, Fox KA, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. *JAMA* 2005; **293**: 2908–17.
- 4 Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007; **357**: 2001–15.
- 5 Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; **361**: 1045–57.
- 6 Bhatt DL, Lincoff AM, Gibson CM, et al. Intravenous platelet blockade with cangrelor during PCI. *N Engl J Med* 2009; **361**: 2330–41.
- 7 Harrington RA, Stone GW, McNulty S, et al. Platelet inhibition with cangrelor in patients undergoing PCI. *N Engl J Med* 2009; **361**: 2318–29.
- 8 Bhatt DL, Stone GW, Mahaffey KW, et al, for the CHAMPION PHOENIX Investigators. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med* 2013; **368**: 1303–13.
- 9 Steg PG, Bhatt DL, Hamm CW, et al, for the CHAMPION Investigators. Effect of cangrelor on periprocedural outcomes in percutaneous coronary interventions: a pooled analysis of patient-level data. *Lancet* 2013; published online Sept 3. [http://dx.doi.org/10.1016/S0140-6736\(13\)61615-3](http://dx.doi.org/10.1016/S0140-6736(13)61615-3).
- 10 Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001; **358**: 527–33.
- 11 Sabatine MS, Cannon CP, Gibson CM, et al. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. *JAMA* 2005; **294**: 1224–32.
- 12 Steinhubl SR, Berger PB, Mann JT 3rd, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002; **288**: 2411–20.
- 13 Mehta SR, Tanguay JF, Eikelboom JW, et al. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. *Lancet* 2010; **376**: 1233–43.
- 14 Parodi G, Valenti R, Bellandi B, et al. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. *J Am Coll Cardiol* 2013; **61**: 1601–06.
- 15 Mehta SR, Granger CB, Boden WE, et al. Early versus delayed invasive intervention in acute coronary syndromes. *N Engl J Med* 2009; **360**: 2165–75.



## Tracking the transmission and evolution of MERS-CoV

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In 2012, Middle East respiratory syndrome coronavirus (MERS-CoV) first emerged in a patient who died of severe pneumonia in Saudi Arabia.<sup>1</sup> Although most cases confirmed so far in the Middle East have been sporadic with an unknown source of infection, human-to-human transmission has been reported in health-care and household settings.<sup>2–4</sup> However, the source of the virus and mode of disease transmission remain unknown

despite detection of a small fragment of sequence identical to the EMC/2012 MERS-CoV in a *Taphozous perforatus* bat captured in Saudi Arabia<sup>5</sup> and reports of cross-reactive antibodies to MERS-CoV in dromedary camels in Oman and the Canary Islands.<sup>6</sup>

A hospital outbreak of MERS in the eastern province of Saudi Arabia was previously described,<sup>3</sup> with full genome analysis of four isolates of the Al-Hasa

outbreak combined with five previously identified MERS-CoV genomes. The investigators estimated that the time of most recent common ancestor (tMRCA) was August, 2011 (95% highest posterior density [HPD] November, 2009 to April, 2012), and showed that the four viruses formed a monophyletic clade. The study provided a better understanding of the transmission of MERS-CoV within family clusters<sup>2,7</sup> and in health-care settings.<sup>4</sup> Nevertheless, the four cases selected were closely linked epidemiologically within this outbreak involving four health-care facilities.<sup>3</sup>

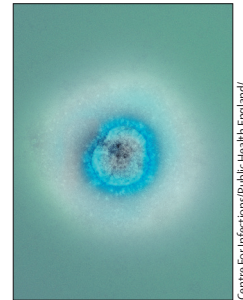
In *The Lancet*, Matthew Cotten and colleagues<sup>8</sup> further describe the geographical distribution and phylogenetic relation of MERS-CoV infections across time in Saudi Arabia. This study represents the largest number of MERS-CoV genomes described so far, with 13 complete and eight partial genomes (30–95% genome coverage) from 21 clinical MERS samples taken from the Al-Hasa outbreak and four other sites in Saudi Arabia (Riyadh, Buraidah, Bisha, and Hafr-Al-Batin). Each of the sequences was derived directly from clinical specimens of patients and thus avoided any mutations that would be introduced by tissue culture passage. The authors report three distinct MERS-CoV genotypes, whereas phylogeographic analyses suggest that the MERS-CoV zoonotic reservoir is geographically dispersed. Furthermore, genetic diversity in the Al-Hasa cluster suggests that the hospital outbreak might have been caused by more than one virus introduction. The data obtained from clinical MERS samples from the Al-Hasa cluster and community outbreaks has recorded evolution of the MERS-CoV virus in this epidemic within Saudi Arabia, and the sequence variations also reveal remarkable multiple-tree clusters. The study has provided interesting data supporting circulation of MERS-CoV since the middle of 2011, with the estimated tMRCA as July, 2011 (95% HPD July, 2007 to June, 2012).<sup>8</sup>

Although the human exposures that result in infection remain unknown, this study has added the novel finding of three distinct MERS-CoV genotypes in Riyadh, with at least two distinct lineages probably circulating in Riyadh in October, 2012. Disease transmission patterns in the epidemic suggest both human-to-human transmission and sporadic zoonotic events. The current genome sequence set is not adequate to discriminate definitively between single or multiple zoonotic introductions, but the

description of the pair of related genomes from Riyadh and Bisha and the description of cases in east and west Saudi Arabia in both major lineages of the tree suggest many zoonotic events. Overall, this is an interesting study that extends earlier findings.<sup>2,3</sup> Although this report provides neither direct evidence of animal transmission nor the precise mechanism of transmission, the information is useful in tracing the source and transmission of MERS-CoV.<sup>8</sup>

There are some examples of the historical role and scientific value of molecular methods in tracing emerging severe acute respiratory infections. After the major outbreaks of SARS-CoV in 2003, researchers in many countries had applied molecular genome analysis to track the viral evolution and spread of the disease.<sup>9–11</sup> PCR has provided the scientific basis for direct examination of clinical samples for evidence of infection. Similar to MERS-CoV, sequence variations were reported in SARS-CoV obtained from different patients in this epidemic.<sup>9–11</sup> Cotten and colleagues<sup>8</sup> have effectively shown that sequence variations in the MERS-CoV genome can be applied as a powerful molecular method in tracing the route of transmission, when used in conjunction with standard epidemiology. Furthermore, using the publicly released full genomic sequences of SARS-CoV in 2003, various molecular detection methods based on RT-PCR were developed. Most of the diagnostic assays were initially focused on RNA extracted from nasopharyngeal aspirates, urine, and stools, but assays based on the analysis of RNA extracted from plasma and serum were later developed.<sup>12,13</sup> Such blood RNA assays (with one targeted at the nucleocapsid region and the other the polymerase region of the virus genome) allowed the more standardised quantitative expression of viral loads and became useful for early SARS diagnosis, with a detection rate of up to 80% during the first week of illness, when serology diagnosis of SARS was not sensitive at the early stage.<sup>12,13</sup> These quantitative systems, if available, might be useful for the early diagnosis of MERS-CoV and can provide viral load information that might facilitate prognostic assessments of an infected individual.

With the increasing number of sporadic cases of MERS in the Middle East, more research is needed into the mode of transmission and exposures responsible for the sporadic introductions of MERS-CoV into human populations. Development of rapid and reliable



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diagnostic assays is also urgently needed so that health authorities can take appropriate public health measures to interrupt disease transmission and contain the virus.

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I declare that I have no conflicts of interest.

- 1 Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med* 2012; **367**: 1814–20.
- 2 Memish ZA, Zumla AI, Al-Hakeem RF, Al-Rabeeh AA, Stephens GM. Family cluster of Middle East respiratory syndrome coronavirus infections. *N Engl J Med* 2013; **368**: 2487–94.
- 3 Assiri A, McGeer A, Perl TM, et al. Hospital outbreak of Middle East respiratory syndrome coronavirus. *N Engl J Med* 2013; **369**: 407–16.
- 4 Guery B, Poissy J, el Mansouf L, et al. Clinical features and viral diagnosis of two cases of infection with Middle East respiratory syndrome coronavirus: a report of nosocomial transmission. *Lancet* 2013; **381**: 2265–72.
- 5 Memish Z, Mishra N, Olival K, et al. Middle East respiratory syndrome coronavirus in bats, Saudi Arabia. *Emerg Infect Dis* 2013; published online Aug 23. DOI:10.3201/eid1911.131172.
- 6 Reusken CB, Haagmans BL, Muller MA, et al. Middle East respiratory syndrome coronavirus neutralising serum antibodies in dromedary camels: a comparative serological study. *Lancet Infect Dis* 2013; published online Aug 8. [http://dx.doi.org/10.1016/S1473-3099\(13\)70164-6](http://dx.doi.org/10.1016/S1473-3099(13)70164-6).
- 7 HPA UK Novel Coronavirus Investigation team. Evidence of person-to-person transmission within a family cluster of novel coronavirus infections, United Kingdom, February 2013. *Euro Surveill* 2013; **18**: 20427.
- 8 Cotten M, Watson SJ, Kellam P, et al. Transmission and evolution of the Middle East respiratory syndrome coronavirus in Saudi Arabia: a descriptive genomic study. *Lancet* 2013; published online Sept 20. [http://dx.doi.org/10.1016/S0140-6736\(13\)61887-5](http://dx.doi.org/10.1016/S0140-6736(13)61887-5).
- 9 Chim SS, Tsui SK, Chan KC, et al. Genomic characterisation of the severe acute respiratory syndrome coronavirus of Amoy Gardens outbreak in Hong Kong. *Lancet* 2003; **362**: 1807–08.
- 10 Chiu RW, Chim SS, Lo YM. Molecular epidemiology of SARS—from Amoy Gardens to Taiwan. *N Engl J Med* 2003; **349**: 1875–76.
- 11 Guan Y, Peiris JS, Zheng B, et al. Molecular epidemiology of the novel coronavirus that causes severe acute respiratory syndrome. *Lancet* 2004; **363**: 99–104.
- 12 Ng EK, Ng PC, Hon KL, et al. Serial analysis of the plasma concentration of SARS coronavirus RNA in pediatric patients with severe acute respiratory syndrome. *Clin Chem* 2003; **49**: 2085–88.
- 13 Ng EK, Hui DS, Chan KC, et al. Quantitative analysis and prognostic implication of SARS coronavirus RNA in the plasma and serum of patients with severe acute respiratory syndrome. *Clin Chem* 2003; **49**: 1976–80.

## Effects of a short-term mass-media campaign against smoking

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Although the benefits of continuous antismoking media campaigns are clear,<sup>1</sup> little is known about the effects of short-term programmes on attempts to quit smoking by the general population. In *The Lancet*, Timothy McAfee and colleagues<sup>2</sup> report on a national antismoking campaign funded by the US Centers for Disease Control and Prevention, called “Tips from Former Smokers” (Tips), which was delivered via television, print, digital, and other media outlets for 3 months. Development of advertisements for the Tips campaign was rigorous and considered a diverse set of smokers’ opinions about what would help them quit. Hard-hitting, emotional, and graphic real-life stories were produced that emphasised the effects of smoking-related disease on quality of life, rather than focusing on risk of death.

The effectiveness of this public-health education programme was assessed by baseline and follow-up surveys of a nationally representative sample of 3051 adult smokers and 2220 non-smokers. The prevalence of smokers reporting a quit attempt rose over the period of the campaign (adjusted odds ratio 1.20, 95% CI 1.02–1.40;  $p=0.02$ ). McAfee and colleagues estimated that, nationwide, 1.64 million additional smokers made a quit attempt during the 3-month Tips campaign, and 220 000

(95% CI 159 000–282 000) remained abstinent at follow-up. Furthermore, 4.7 million additional non-smokers recommended a cessation service (telephone helpline or quit assistance website) and more than 6 million discussed the hazards of smoking with family and friends. These study findings could be deemed population-specific, but they should nonetheless encourage low-income and middle-income countries that are facing major tobacco epidemics—such as China, India, Bangladesh, Egypt, Malaysia, Indonesia, and Russia—to develop appropriate and cost-effective strategies for tobacco control.<sup>3</sup>

Tobacco dependence has been defined as a chronic disease,<sup>4</sup> and the process of quitting smoking is dynamic; therefore, a prolonged campaign might have had a greater effect. Globally, many long-term anti-smoking programmes have been delivered.<sup>1,5</sup> However, Tips was the first federally funded, high-exposure, national antismoking media campaign in the USA, and it reached almost 80% of the US population. McAfee and colleagues used a conservative approach to estimate the possible long-term effect of the Tips campaign. Their findings suggested that more than 100 000 smokers were likely to have become sustained quitters because of the Tips campaign, possibly adding a