that was commissioned by the World Health Organization to the Cochrane Collaboration. In addition, we will upload the summary results to the trial registry as allowed by the ChiCTR platform. Winter is coming, so planning for a new wave of the COVID-19 pandemic becomes extremely urgent. We must complete the multicenter, randomized controlled clinical trial as soon as possible; otherwise, we have to withdraw this registration from the website by the end of 2020.

Two publications sharing the same registration number is not appropriate, although they are closely related and have been registered at ChiCTR and the National Medical Research Registration Information System with the identical number. We will consult the Ethics Committee and resolve the issue.

Mengmei Wang and Ke Hu

Department of Respiratory and Critical Care Medicine, Renmin Hospital of Wuhan University, Wuhan, China

References

1. Wang M, Zhao Y, Hu W, et al. Treatment of COVID-19 patients with prolonged post symptomatic viral shedding with leflunomide—a single-center, randomized, controlled clinical trial. Clin Infect Dis **2020**; doi:10.1093/cid/ciaa1417.
2. Xiong R, Zhang L, Li S, et al. Novel and potent inhibitors targeting DHODH are broad-spectrum antivirals against RNA viruses including newly-emerged coronavirus SARS-CoV-2. Protein Cell **2020**; 11:723–39.
3. Hu K, Wang M, Zhao Y, et al. A small-scale medication of leflunomide as a treatment of COVID-19 in an open-label blank-controlled clinical trial. Virol Sin **2020**; 21:1–9.
4. Chinese Clinical Trial Registry. A multicenter, randomized, double-blind, controlled clinical trial for leflunomide in the treatment of novel coronavirus pneumonia (COVID-19). **2020**. Available at: http://www.chictr.org.cn/showprojen.aspx?proj=49831. Accessed 22 February 2020.

Correspondence: K. Hu, Renmin Hospital of Wuhan University, Wuhan, China (huke-rmhospital@163.com).

Differential Household Attack Rates Mirror the Ability to Control Coronavirus Disease 2019 (COVID-19)

TO THE EDITOR—The inability of the United States and most of Europe to replicate the successes observed across Asia in controlling the severe acute respiratory syndrome coronavirus 2 outbreak has led to spiralling infection rates, repeated lockdowns in Europe, and no sign of rounding the turn. In contrast, many Asian and Pacific countries are currently enjoying a semblance of normality. The study by Lewis et al [1] points to one of the causes for these differences.

They find the household secondary attack rate (HSAR) to be around 30% in Utah and Wisconsin in the United States, through the monitoring of household contacts of cases. This echoes another recent paper by Grijalva et al [2] for households in Wisconsin and Tennessee, who estimate the HSAR to be 30% to 50%, depending on whether those infected on enrollment are included in the definition.

In contrast, large household studies in China and Singapore found household attack rates to be less than one-half of their American counterparts: Ng et al [3] showed an HSAR of around 12% in Singapore, whereas Bi et al [4] estimated it to be 11% in Shenzhen. The difference is not attributable to underascertainment, as Ng et al confirmed infection status through serology.

We believe that a fundamental difference in case management lies behind these differences. In Singapore, all coronavirus disease 2019 (COVID-19) cases, regardless of severity, are isolated in a healthcare facility upon diagnosis, either at a hospital or a converted community facility akin to China's *fangcang* hospitals [5], until they are no longer infectious. No cases are isolated at home. Cases are managed similarly in China.

We previously argued on theoretical grounds [6] that isolation—not self-isolation—of cases may reduce the
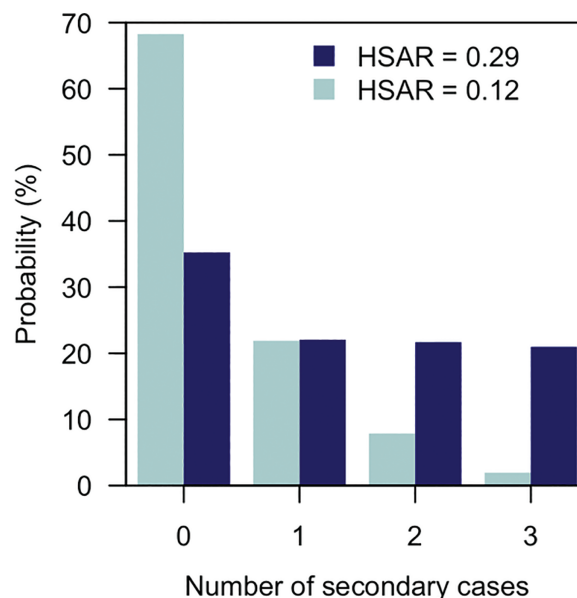

Figure 1. Number of additional infections in households of 4 members with a single index case, when the household secondary attack rate (HSAR) is 0.29 (based on Lewis et al [1]) or 0.12 (based on Ng et al [3]). Probabilities are from a chain-binomial model [7]. The average number of secondary cases in the HSAR = 0.29 case is 1.3; for HSAR = 0.12, it is 0.4.

reproduction number sufficiently to reduce the size of outbreaks. Chain-binomial models (Figure 1) show that reduced HSAR leads to remarkable reductions in secondary household cases—an HSAR of 30% creates an estimated 1.3 secondary infections, whereas 12% creates just 0.4. Given the need to reduce transmission to less than 1 secondary case per index case for epidemic control, otherwise described as an effective R_0 of below 1, this difference may explain why the epidemic continues to run amok in the United States.

For infection control of methicillin-resistant *Staphylococcus aureus* in hospitals, it is established that colonized cases (ie, those without disease and at low risk of complications) should be cohorted to prevent onward transmission, which protects potentially vulnerable inpatients. This principle is not to benefit colonized patients, who may never develop disease, but those around them. Using the same principle, mild COVID-19 cases ought to be moved out of the household until they no longer pose a threat of transmitting infection.

If a country does not follow fundamental infection control principles in the COVID-19 pandemic, it is scarcely a surprise if it fails to control infection.

Notes

Alex R. Cook,[1] Borame L. Dickens,[1] and Annelies Wilder-Smith[2,3,4,]

[1]Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore, [2]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, [3]Department of Disease Control, London School of Hygiene & Tropical Medicine, London, UK, and [4]Heidelberg Institute of Global Health, University of Heidelberg, Germany

References

1. Lewis NM, Chu VT, Ye D, et al. Household transmission of SARS-CoV-2 in the United States. Clin Infect Dis 2020. doi:10.1093/cid/ciaa1166.
2. Grijalva CG, Rolfes MA, Zhu Y, et al. Transmission of SARS-COV-2 infections in households—Tennessee and Wisconsin, April-September 2020. MMWR Morb Mortal Wkly Rep 2020; 69:1631–4.
3. Ng OT, Marimuthu K, Koh V, et al. SARS-CoV-2 seroprevalence and transmission risk factors among high-risk close contacts: a retrospective cohort study. Lancet Infect Dis 2020. doi:10.1016/S1473-3099(20)30833-1.
4. Bi Q, Wu Y, Mei S, et al. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study. Lancet Infect Dis 2020; 20:911–9.
5. Fang D, Pan S, Li Z, et al. Large-scale public venues as medical emergency sites in disasters: lessons from COVID-19 and the use of Fangcang shelter hospitals in Wuhan, China. BMJ Glob Health 2020; 5. doi:10.1136/bmjgh-2020–002815.
6. Dickens BL, Koo JR, Wilder-Smith A, Cook AR. Institutional, not home-based, isolation could contain the COVID-19 outbreak. Lancet 2020; 395:1541–2.
7. Bailey NTJ. The use of chain-binomials with a variable chance of infection for the analysis of intra-household epidemics. Biometrika 1953; 40:279–86.

Correspondence: B. L. Dickens, National University Hospital, Singapore, Singapore, Singapore (ephdbsl@nus.edu.sg; bdickens@ymail.com).

How Second-Line Injectable Drugs Work

TO THE EDITOR—The meta-analysis by Cegielski and colleagues on the effectiveness of second-line injectable drugs (SLID) adds nuance to the previously published meta-analysis, which showed a surprising lack of activity [1, 2]. However, we have concerns with regards to the outcomes evaluated and thus with the conclusions of both meta-analyses.

The meta-analyses studied recurrence (treatment failure or relapse) and mortality [1, 2]. These outcomes are almost entirely dependent on the core drug, for example, fluoroquinolone or bedaquiline, driving the efficacy of rifampicin-resistant tuberculosis (RR-TB) treatment [3]. Without active core drug in the regimen, success is rare [4]. SLID are not core drugs because they have no sterilizing power [3]. SLID act only in alkaline environment where they rapidly kill actively replicating bacilli. They provide the most effective protection of the core drug against acquired drug resistance (ADR) [5], by preventing the selection of newly emergent or initially present core drug-resistant bacilli [3]. When evaluating the effect of SLID, the endpoint should thus be acquired core drug resistance in patients with initially core drug-susceptible TB. This explains why no or little effect of SLID on recurrence was seen in patients with initially fluoroquinolone-resistant RR-TB treated with a fluoroquinolone-based regimen [1]. Indeed, SLID are only successful when combined with an active core drug [5, 6].

The authors acknowledge that their finding of kanamycin's ineffectiveness could be due to its infrequent use with a more potent later generation fluoroquinolone, which were more frequently combined with amikacin [1]. The type of fluoroquinolone that acts as core drug must be taken into account when assessing the effect of SLID because of the different resistant mutant suppression windows [7, 8]. Almost nonexistent for the earlier drugs, it is considerable for fourth-generation fluoroquinolones, with differences also within the group [9]. Gatifloxacin was better than levofloxacin or moxifloxacin in overcoming its own lower-level resistant mutants. Used with kanamycin for the first 4 months, it ensured that none of the 859 patients successively treated with the standard short RR-TB regimen experienced recurrence with fluoroquinolone ADR [10]. However, reduction of standard 4-month administration of kanamycin to 2 months significantly increased the risk of gatifloxacin ADR [5]. That kanamycin