Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

use of combination therapy, including with non-study antibiotics.

The investigators noted no differences in antibiotic use between randomisation groups, and study antibiotics accounted for 42% and 43% of all antibiotics used in the cycling and mixing groups, respectively. For the primary endpoint, investigators did not find a significant difference in the mean prevalence of antibiotic-resistant, Gram-negative bacteria (168 [23%] patients with carriage during cycling *vs* 184 [22%] during mixing) even when considering the incidence rate ratio derived from a mixed effects analysis adjusted for potential confounders (1·039, 95% CI 0·837–1·291, p=0·73). No difference was observed in several subgroup analyses. These results thus strongly suggest that cycling of antibiotics has no beneficial effect over antibiotic mixing against the emergence of antibiotic resistance for Gram-negative bacteria.

Where does this trial leave us? This study had a negative outcome, but the findings are consistent with theoretical arguments.[5] However, a negative study can still be highly informative if the study quality was high, meaning sufficient statistical power to avoid a type II error, high protocol adherence, and a thorough statistical analysis accounting for potential biases. The trial reported by van Duijn and colleagues fulfils these criteria. In their study protocol, the investigators predefined the statistical approach using different sensitivity analyses with sufficient power to detect effects if any were present. High adherence to the study protocol was observed despite two major deviations (one in which data were excluded due to missing point-prevalence information, and another in which the washout period was prolonged due to an outbreak of carbapenem-resistant *Klebsiella pneumoniae*). There is, therefore, no obvious reason that another trial would contradict these findings. However, reduction of the prevalence of antibiotic-resistant, Gram-negative bacteria in ICUs remains a priority; there is an urgent need to find new institutional strategies that prove beneficial in clinical trials. Until then, we need to reinforce the patient-level tools that are available, including (among others) improved hand hygiene and better selection of patients in need of antibiotics by host-response markers such as procalcitonin and other pathogenic markers.[10,11]

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Herd immunity: hyperimmune globulins for the 21st century

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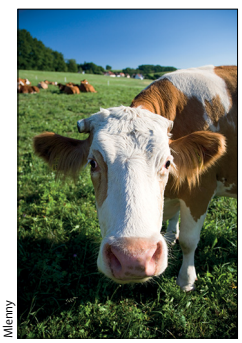
See **Articles** page 410

Recent headlines, including outbreaks of Ebola virus disease in urban west Africa, the intercontinental transmission of Middle East respiratory syndrome virus (MERS) from the Arabian Peninsula to South Korea, and the emergence of Zika virus as a fetal neurotoxic agent, highlight the global threat posed by emerging infectious diseases in an increasingly connected world.

In use since the late 1800s, convalescent blood products are some of the oldest instruments in the expanding toolbox of immune therapies for infectious



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See Online for appendix

disease. Passive transfer of convalescent human sera has been investigated for protection against coronaviruses (severe acute respiratory syndrome), arenaviruses (Lassa, Junin), filoviruses (Ebola, Marburg), and pandemic influenza viruses (H5N1, H1N1).[1] However, positive findings have not been substantiated by controlled trials. Few immunoglobulins are licensed for infectious disease and passive transfer is not without some attendant risks (appendix). Heterologous equine and ovine immune globulins can induce hypersensitivity; Fab and $F(ab')_2$, which have shorter in-vivo half-lives, lessen hypersensitivity, suggesting this hypersensitivity is largely mediated by foreign Fc. Although human IgG is desirable, the risk of transmitting unidentified pathogens and costly donor screening protocols are barriers to use of fractionated human immune plasma products. For example, clinical studies of anti-MERS intravenous immunoglobulin reported difficulty identifying human plasma donors because of low neutralising titres in convalescent patients and the generally short-lived nature of neutralising antibody responses after coronavirus infection.[2]

In *The Lancet Infectious Diseases*, John Beigel and colleagues report results from a first-in-human phase 1 clinical trial of the safety and tolerability of SAB-301, a fully human polyclonal IgG developed from plasma of transchromosomic cattle immunised with MERS spike protein nanoparticles.[3] The transchromosomic cattle used to produce SAB-301 were developed over the course of a decade in a remarkable feat of genetic engineering (figure). In research studies, multiple vaccine platforms have generated antigen-specific human IgG in transchromosomic cattle. Hyperimmunisation of transchromosomic cattle with anthrax protective antigen yields human neutralising antibodies that protect mice against anthrax challenge.[4] Additionally, DNA vaccination yields human neutralising antibodies with demonstrated efficacy after passive transfer to rodent models of Ebola virus and hantavirus infection.[5,6] Immunisation with recombinant nanoparticles used in the production of SAB-301 or with gamma-irradiated whole-killed virions induced anti-MERS neutralising human IgG in transchromosomic cattle, which reportedly reduce lung viral load in a non-lethal murine MERS challenge.[7]

In their study, Beigel and colleagues show that human participants who received infusion of SAB-301 developed anti-MERS neutralising antibody titres that correlated with serum SAB-301 concentrations. These titres were achieved without clinically significant hypersensitivity or adverse events at infusion rates below current intravenous immunoglobulin guidelines. The SAB-301 terminal elimination half-life appears to be within range of a typical human antibody. SAB-301 is enriched in human IgG1κ, which could exhibit important in-vivo effector-mediated functions in addition to demonstrated in-vitro neutralising capability.[8] The effect of bovine processes on SAB-301 human IgG development is unclear. Comparative immunology of human beings and cattle point to several key innate immune factors—namely, anatomical (eg, a primary lymphoid organ in the bovine intestine referred to as

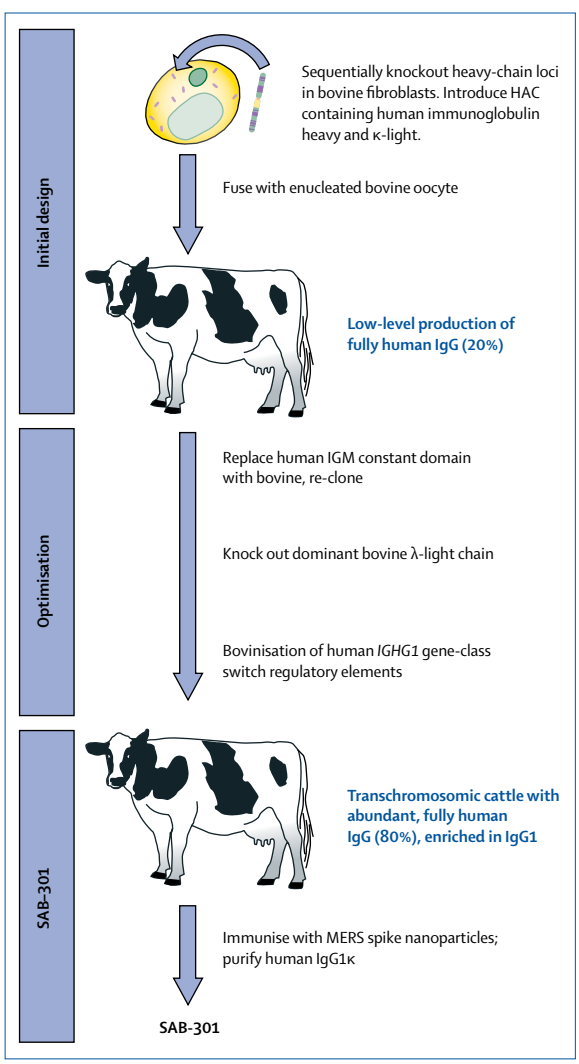

Figure: **SAB-301 production in transchromosomic cattle**
MERS=Middle East respiratory syndrome. HAC=human artificial chromosome. IGM=immunoglobulin heavy constant μ. IGHG1=immunoglobulin heavy constant gamma 1.

an ileal Peyer's patch[9]), cellular (eg, abundant bovine circulatory γδ T cells with unique capabilities[10]), and molecular (eg, bovine pattern recognition receptor function[11]) factors, which could lead to distinct adaptive immunity. Post-translational modifications, including glycosylation,[4] could lead to dissimilar effector functions between transchromosomic IgG and human IgG, and will require additional work to be understood. Transchromosomic cattle reportedly make 150–600 g of human IgG per animal per month,[7] thus more than 6500 cows would be needed to produce an immediate 50 mg/kg dose of unfractionated human IgG for one million adults. Potent, functional, antigen-specific antibody generation through optimised vaccination protocols will be crucial for environmental and economic feasibility of this platform. The therapeutic and protective efficacy of SAB-301 in human infection or lethal animal challenge has not been reported, underscoring that this is an early technology requiring further clinical investigation.

Vitality in the field of antibodies deployed against infectious diseases is supported by the concomitant rise in systems for rapid delivery of rigorously selected and highly potent monoclonal antibodies as proteins, DNA, or RNA, as well as vectored delivery. Additional technologies addressing the need for sustainable, potent antibody therapies include engineered bispecific antibodies and half-life extension modifications. The study of transchromosomic cattle with the ability to produce polyclonal antibody responses against emergent pathogens advances a platform worthy of further consideration, possibly in outbreak situations as well as for protection of at-risk populations.

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The long road towards a safe and effective treatment of chronic Chagas disease

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See **Articles** page 419

Chagas disease, a chronic systemic parasitosis by the kinetoplastid protozoon *Trypanosoma cruzi*, is the leading cause of cardiac morbidity and mortality in poor rural and suburban areas of Latin America and the source of the largest parasitic disease burden in the American continent. This burden is now spreading worldwide owing to international migration.[1,2] A recent change in the scientific understanding of the pathogenesis of chronic Chagas disease has led to consensus that all *T cruzi*-seropositive patients should receive aetiological treatment with anti-*T cruzi* drugs.[3] Currently available drugs, the nitroheterocyclic compounds benznidazole and nifurtimox, were developed empirically over 40 years ago and are effective in acute, congenital, and early chronic (paediatric) Chagas disease, but observational studies in prevalent established chronic disease indicated that their efficacy is substantially lower and variable; furthermore, recipients of either drugs commonly experience adverse effects that can lead to treatment discontinuation in 10–30%.[2,4]