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studies of transmission and efficiency in the conduct of prevention trials.

Contributors
M T Dorak participated in data analysis, interpretation of results, and preparation of the manuscript. J Tang and E S Lobashevsky were responsible for HLA typing, laboratory data acquisition and management, and contributed to analysis and preparation of the manuscript. A Pennan-Aguilar, A O Westfall, and M M Schaeen were responsible for statistical analysis and management of the full dataset and reviewing of the final version of the manuscript. I Zulu and N G Kancheya assisted with protocol development and assembling of the participants, supervised onsite collection of epidemiological data and biological specimens, and reviewed the latest version of the manuscript. S A Allen and R A Kaslow designed the original study and framework for immunogenetics analyses, supervised collection of relevant clinical and epidemiological data and biological specimens, data analysis and interpretation, and reviewed successive drafts of the manuscript.

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None declared.

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Human monoclonal antibody as prophylaxis for SARS coronavirus infection in ferrets
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SARS coronavirus continues to cause sporadic cases of severe acute respiratory syndrome (SARS) in China. No active or passive immunoprophylaxis for disease induced by SARS coronavirus is available. We investigated prophylaxis of SARS coronavirus infection with a neutralising human monoclonal antibody in ferrets, which can be readily infected with the virus. Prophylactic administration of the monoclonal antibody at 1.0 mg/kg reduced replication of SARS coronavirus in the lungs of infected ferrets by 3·3 logs (95% CI 2·6–4·0 logs; p<0.001), completely prevented the development of SARS coronavirus-induced macroscopic lung pathology (p=0·013), and abolished shedding of virus in pharyngeal secretions. The data generated in this animal model show that administration of a human monoclonal antibody might offer a feasible and effective prophylaxis for the control of human SARS coronavirus infection.

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Severe acute respiratory syndrome (SARS) has emerged as a frequently fatal respiratory-tract infection caused by the newly identified SARS coronavirus. After the worldwide SARS epidemic in 2002–2003, sporadic cases continue to arise in southern China, possibly because of human contact with a newly identified SARS coronavirus. After the worldwide SARS epidemic in 2002–2003, sporadic cases continue to arise in southern China, possibly because of human contact with a newly identified SARS coronavirus.
with the animal reservoir. Two recent cases of laboratory-acquired SARS coronavirus infections in China spread into the community and triggered extensive efforts in tracing and isolating contacts of patients to prevent a new epidemic. Means to control SARS coronavirus infection through active or passive immunisation are, therefore, urgently needed.

Passive transfer of mouse immune serum has been shown to reduce pulmonary viral titres in mice infected with SARS coronavirus. Immunoprophylaxis of SARS coronavirus infection with human monoclonal antibodies might therefore be a viable strategy to control SARS.

We generated a human IgG1 monoclonal antibody, CR3014, reactive with whole inactivated SARS coronavirus, by antibody phage display technology screening a large naive antibody library. Binding of this antibody to the viral peplomers was visualised by electron microscopy with a 10× objective. For measurement of the SARS coronavirus titre, homogenates were prepared from 0.1–0.3 g of lung tissue pooled from cranial, medial, and caudal parts of the lung. Histologically lesions consisted mainly of mild alveolar damage as well as peribronchial and perivascular lymphocyte infiltration. RT-PCR on pharyngeal swabs showed that virus was shed in the throat throughout day 7. Animals exposed to the mixture of virus and CR3014 had almost undetectable titres of SARS coronavirus in the lung, showed no lung lesions on day 4 or 7, and did not shed SARS coronavirus in their throats.

In the second set of experiments, two groups of ferrets (n=4 in each group) received an intraperitoneal injection of either CR3014 or the control antibody at a concentration of 10 mg/kg, 24 h before intratracheal infection with 10^5 TCID_50. SARS coronavirus strain HKU-39849, strain HKU-39849. Venous blood was drawn before administration of monoclonal antibody, before challenge, and on day 2 after the challenge. We measured the human IgG1 content of the serum by ELISA, and the neutralising capacity by a neutralisation assay using the fixed virus-varying serum-dilution format. Pharyngeal swabs were taken from the animals before the inoculation and on days 2 and 4 after the challenge for qualitative RT-PCR. Two animals from each of the four groups were killed on days 4 and 7 and necropsies were done according to a standard protocol. For assessment of lung inflammation associated with SARS coronavirus infection, haematoxylin-eosin-stained sections from the cranial and caudal parts of the lung were examined for inflammatory foci by light microscopy with a 10× objective. For measurement of the SARS coronavirus titre, homogenates were prepared from 0.1–0.3 g of lung tissue pooled from cranial, medial, and caudal parts of the lung.

All control ferrets had high titres of SARS coronavirus in their lungs on day 4, and lower titres on day 7. Viral replication was accompanied by multifocal pulmonary lesions affecting about 5–10% of the surface area of the lung. Histologically lesions consisted mainly of mild alveolar damage as well as peribronchial and perivascular lymphocyte infiltration. RT-PCR on pharyngeal swabs showed that virus was shed in the throat throughout day 7. Animals exposed to the mixture of virus and CR3014 had almost undetectable titres of SARS coronavirus in the lung, showed no lung lesions on day 4 or 7, and did not shed SARS coronavirus in their throats.
of the control animals (95% CI 2·6–4·0 logs, p<0·001 [Student’s $t$ test]; figure 2A). This difference was accompanied by complete protection from macroscopic lung pathology (p=0·013 [Wilcoxon rank-sum test]; figure 2C) and a reduction of microscopic lesions compared with controls, which all showed multifocal lesions on gross necropsy (figure 2D). Shedding of SARS coronavirus in the throat was completely abolished in three of the four animals treated with CR3014 (figure 2B). However, in one animal the level of SARS coronavirus excretion was similar to that noted in the control group. The concentration of CR3014 in the serum of this ferret before challenge was less than 5 μg/mL, compared with 65–84 μg/mL in the other three animals, suggesting inappropriate antibody administration. Neutralising serum titres in this animal were less than half of those in the other animals on day 0 (titre of 5 against 100 TCID$_{50}$), and were not detectable on day 2 after infection, compared with a titre of 5–10 against 100 TCID$_{50}$ in the other animals on day 2.

SARS coronavirus has been detected in nasopharyngeal aspirates of up to 72% of SARS patients, being associated with increased mortality, and in the lungs of all autopsied patients by viral isolation or RT-PCR. On the basis of our data and the successful prophylaxis of respiratory syncytial virus disease with a humanised monoclonal antibody (Palivizumab), we reason that immunoprophylaxis of SARS coronavirus infection with a human monoclonal antibody might be an option for the control of SARS. The prophylactic dose we used for CR3014 (10 mg/kg) is less than the 15 mg/kg dose at which Palivizumab is given intramuscularly to at-risk infants once a month. If CR3014 reduced the replication of SARS coronavirus in people to the same extent as in ferrets, and in view of the serum halflife of up to 20 days for IgG1 in human beings, one intramuscular administration of CR3014 at the dose used in this study should protect an adult for the length of at least one to two SARS coronavirus incubation periods (median 4–6 days). Passive immunisation with CR3014 might, therefore, be a feasible approach to prevent lung manifestations in people exposed to SARS coronavirus, and prevent person-to-person spread of the virus by abolishment of viral shedding in pharyngeal secretions.

Contributors
J ter Meulen, A B H Bakker, G J Weverling, J Goudsmit, and A D M E Osterhaus planned the study, analysed data, and wrote the report. E N van den Brink, J de Kruif, W Preiser, and W Spaan generated and characterised the recombinant antibody. H R Gelderblom did electron microscopy. B E E Martina and B L Haagmans did animal experiments and virus titrations. T Kuiken did pathological analysis. All authors saw and approved the final version of the manuscript.

Conflict of interest statement
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