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a cyclical movement characterised by remote outbreaks interspersed with periods of epidemiological silence.⁷ This epidemiological pattern favours a fast immunisation schedule with long-term protection.

Live-attenuated vaccines are currently the most cost-effective health intervention available. Nevertheless, safety and efficacy concerns should continue to be addressed carefully in the next clinical trial phase. Among the adverse effects that have been reported, joint pain and leucopenia (especially neutropenia) keep our attention. Even if already observed with other live-attenuated vaccines, they are also features of CHIKV infection that can have important consequences, especially in older people (ie, aged >50 years) or people with comorbidities. Persistent musculoskeletal symptoms are a hallmark of the chronic phase and might be related to older age and female sex⁸ that were not well represented in this phase 1 study. The safety portfolio should also continue to study shedding of the vaccine and the risk for mosquito transmission. The stability of the attenuated virus, which includes deletion of a large part of the non-structural protein 3 gene, has already been assessed in previous studies.⁹

Even if safety and immunogenicity only were investigated in this study, Wressnigg and colleagues used the high dose of the live-attenuated virus to evaluate the effect of immunisation on viraemia as a tool to predict efficacy of the vaccine. The results are encouraging, with no detectable viraemia after revaccination, but this revaccination does not mimic a challenge, which is not possible with the wildtype virus. The vaccine viraemia has been shown to be significantly lower than for the wildtype strain in the non-human primate study.¹⁰ The neutralising activity of antibodies measured in the study was only against the vaccine strain. These antibodies can be easily tested for cross-neutralisation activity against different wildtype viral strains in vitro to give a rough idea of a protective effect. The magnitude of neutralising antibodies titres might also be less important in the

field, where people might have pre-existing alphavirus immunity.

CHIKV vaccine development is exciting because multiple promising vaccine candidates are in the pipeline. In future, a suitable vaccine might be available for each situation—eg, explosive outbreak, endemic countries, travellers, military, and people with underlying medical conditions. We hope that the difficulty of implementing clinical efficacy trials because of the epidemiological pattern of CHIKV can be overcome, making way for these promising vaccines.

We declare no competing interests.

Marie Mura, *Jean Nicolas Tournier
jean-nicolas.tournier@intradef.gouv.fr

Malaria Biologics Branch, Immunology core, Walter Reed Army Institute of Research, Silver Spring, MD 20910, USA (MM); Microbiology and Infectious Diseases Department, Anti-Infectious Biotherapies and Immunity, Institut de Recherche Biomédicale des Armées, Brétigny-sur-Orge Cedex, France (MM, JNT); and Ecole du Val-de-Grâce, Paris, France (JNT)

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A new dawn for the management of influenza?

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At the time of writing, coronavirus disease 2019 (COVID-19) is the world's focus with a global incidence of more than 4 million cases and more than 300 000 deaths. The USA is the epicentre of the pandemic with more than

1·2 million cases and over 80 000 deaths. These numbers are probably underestimates. However, despite these very troubling times, putting these numbers into some context via a comparison with influenza might be useful.

Influenza first gained global notoriety in 1918 when it was described as causing “havoc, death and desolation of a society fighting a war against nature”.¹ Descriptions of the 1918 influenza pandemic are reminiscent of the pneumonic plague or even poison gas because of the extremely severe illness it caused.¹ Even today, some influenza infections remain serious. The burden of influenza worldwide is staggering, with pneumonia and influenza the leading causes of death from infectious diseases in the USA. Recent estimates regarding influenza in the USA are remarkable and thought-provoking in an era of vaccines. In 2017–18, the number of reported infections was 45 million, and although this number decreased in 2018–19, more than 35 million cases were recorded in that year. The number of hospital admissions associated with influenza was 810 000 in 2017–18 and 490 000 in 2018–19, with 61 099 deaths in 2017–18 and 34 200 deaths in 2018–19.² In addition to this health burden, influenza is responsible for substantial economic burden: in 2003, influenza-related costs in the USA were estimated to be US\$100 billion in direct medical costs, with an overall economic burden amounting to \$87.1 billion, calculated on the basis of projected earnings.³

Influenza can be grouped into subgroups A H1N1, A H3, A not subgrouped, and B. These subtypes have distinct geographical and seasonal distributions. Data collected by WHO for 2020 show subtype A to be responsible for about 55% of infections and type B for about 40% in the USA, whereas subtype A is seen in more than 65% of infections in Europe. These differences could have therapeutic implications (eg, oseltamivir is less effective against type B).⁴

Influenza, like COVID-19, infects the most vulnerable individuals, including people older than 70 years and those with cardiovascular diseases, metabolic conditions, obesity, asthma, and chronic lung disease.⁴ Thus, treatments for influenza must account for the age of the patient, potential comorbidities, and potential subgroups of the virus. Antiviral agents such as amantadine and rimantadine were early therapeutic efforts. However, these drugs were administered via inhalation, thus influencing adherence, which can select for resistance.⁵ In an effort to improve adherence, the neuraminidase inhibitors were developed. Zanamavir was shown to be effective against subgroups A and B, most notably in high-risk patients,⁶ and along with another neuraminidase

inhibitor, peramivir, was administered intravenously.⁷ However, neither of these drugs were of an optimal formulation for patient satisfaction or compliance. Oseltamivir is recommended by the US Centers for Disease Control and Prevention and administered as a tablet or suspension twice a day for 5 days.⁸ In a meta-analysis of nine trials, Dobson and colleagues⁹ showed that oseltamivir alleviates symptoms in a shorter time than do other drugs when compared with placebo.

A novel antiviral class shown to be at least as safe and efficacious as oseltamivir but given via a single dose would be an important progression in the treatment of influenza. In *The Lancet Infectious Diseases*, Michael G Ison and colleagues¹⁰ report the findings of their double-blind, placebo-controlled and oseltamivir-controlled, randomised, phase 3 trial on baloxavir marboxil, a small molecule prodrug of baloxavir acid that is active against influenza A and B. Baloxavir is a selective inhibitor of influenza cap-dependent endonuclease. In adolescent and adult outpatients with uncomplicated influenza who were at high risk of influenza-associated complications, Ison and colleagues compared the safety and efficacy of a single oral dose (40 mg or 80 mg, depending on bodyweight) of baloxavir with that of oseltamivir (75 mg twice daily) given for 5 days or matched placebo. The modified intention-to-treat population of 1163 patients comprised 557 (48%) patients with influenza A H3N2, 484 (42%) with influenza B, 80 (7%) with influenza A H1N1, 14 with mixed infection, and 28 with infections caused by non-typeable viruses. 319 (27%) of 1163 patients were considered to be at high risk of influenza-related complications because they were aged 65 years or older, and most of the participants were adults.

Ison and colleagues found that single-dose baloxavir was superior to placebo and similar to oseltamivir in reducing the duration of illness with influenza. The median time to improvement of influenza symptoms (the primary endpoint) was 73.2 h (95% CI 67.2–85.1) in the baloxavir group, 81.0 h (69.4–91.5) in the oseltamivir group, and 102.3 h (92.7–113.1) in the placebo group. The study also showed that baloxavir was superior to placebo in both influenza A and influenza B cases and to oseltamivir in influenza B cases. Importantly, the study was not powered to compare baloxavir with oseltamivir or for comparisons by influenza subtype. A quicker time to reduction of

For more information on global statistics of COVID-19 from Johns Hopkins University and Medicine Coronavirus Resource Center see <https://coronavirus.jhu.edu/map.html>

symptoms, more rapid cessation of viral shedding, and fewer adverse events, including sinusitis, bronchitis, and nausea, were reported with baloxavir than with placebo. Most of these improved outcomes were seen in those who received their therapy within 0–36 h of symptoms being reported (rather than at timepoints after 36 h).

Despite the sound design and thorough conduct of the study, it has some limitations, such as the absence of immunosuppressed patients, pregnant women, and those with liver dysfunction. Additionally, there were few cases of influenza A H1N1 subgroup infections. However, the results of this study hold considerable promise for an efficacious, well-tolerated single-dose oral therapy for influenza, including in those at high risk of influenza complications.

I report being a paid consultant to various companies not involved in the production of antivirals (Melinta, Summit, Ferring).

Glenn S Tillotson

gtillotson@gstmicro.com

GST Micro, Richmond VA 23231, USA

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Persistence of US measles risk due to vaccine hesitancy and outbreaks abroad

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Results of a measles spatial risk analysis from May, 2019, published in *The Lancet Infectious Diseases*, identified US counties with the highest relative risk of a measles outbreak in 2019.¹ Measles outbreaks have persisted in the USA and globally with over 400 000 cases confirmed in 2019, reversing decades of progress towards measles elimination in many countries.^{2,3} In the USA, 1282 cases of measles were reported in 2019 across 31 states and 94 counties, the most since 1992.⁴

In recent years, a growing vaccine hesitancy movement has contributed to decreasing vaccination rates in Europe and the USA.⁵ In the USA, the national vaccination rate is 94.7%, representing good coverage on average.⁶ However, even if a state has an average vaccination rate that is higher than the threshold for herd immunity, outbreaks can still occur if there exist localised communities with a high proportion of unvaccinated individuals. If such communities are highly connected by travel to regions experiencing large outbreaks, then risk of outbreaks in these communities is increased.

Decreasing vaccination rates, combined with an increase in measles outbreaks abroad and high volumes of international travel, places the USA at increased risk of measles introduction and local outbreaks. In response to these persistent risk factors, we expanded upon our previous work¹ to identify the set of US counties at highest risk of measles outbreaks. The risk to each county was computed with a multiplicative function of four factors: incidence rate of measles at travel origin, international air travel volume from each such origin to a US destination county, measles, mumps, and rubella (MMR) vaccination rates in the county, and county population. This study extends the previous study by using a spatial diffusion model to distribute arriving travellers to US counties near international airports (including counties without an airport), and a comprehensive county-level MMR vaccination rate dataset for 40 states. The final risk measure can be interpreted as the expected relative size of measles outbreak in each county.