Race against the Virus

Fear is circling the globe faster than the virus itself. **PANDEMIC**—the word alone evokes a feeling of helplessness. However, rational analysis and careful preparation help to minimize risks.

Influenza A is classified into the subtypes 16 H and 9 N. A/H1N1 = “New Flu”

PHOTOGRAPHY: PICTURE-ALLIANCE/DPA

“THE WORLD IS NOW at the start of the 2009 influenza pandemic,” announced WHO Director General Margaret Chan in a statement to the press in Geneva, Switzerland, on June 11, 2009. “Further spreading is considered inevitable.” What had long been predicted has now come to pass, and many people have been vacillating between two opposing emotions ever since. On the one hand there is concern—to many the word “pandemic” implies a horrible plague. Constant references are made to the horrors of the Spanish flu of 1918, which virtually wiped out entire villages. Factories, schools, businesses, and government offices remained empty. Crops rotted in the fields and livestock starved in their stalls. Between 25 and 50 million people died worldwide.

On the other hand, many others are rubbing their eyes in disbelief—the “new flu” (Influenza A/H1N1) is mild in most cases and often requires no treatment at all. In light of these facts, many of the headlines are puzzling. Why are children with the new flu at a children’s hospital in Ravensburg, Germany, being treated by masked personnel in protective suits, and why are their entire families being placed under quarantine when the course of the illness is not much more than two days of diarrhea?

An eight-member gene team

One reason for the confusion is that hardly anyone knows what the word “pandemic” actually means. Even the experts are not in total agreement. Jeffery Taubenberger of the National Institutes of Health in the U.S. argues that the pandemic began 91 years ago. At that time a new type of virus that could also infect humans originated in birds. The Spanish flu pathogen established a virus dynasty that continues to exist today. According to Taubenberger, all Influenza A viruses that have adapted to humans are descendants of this one virus, including those responsible for pandemics as well as those responsible for the annual waves of flu.

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Masks offer protection in crowds.

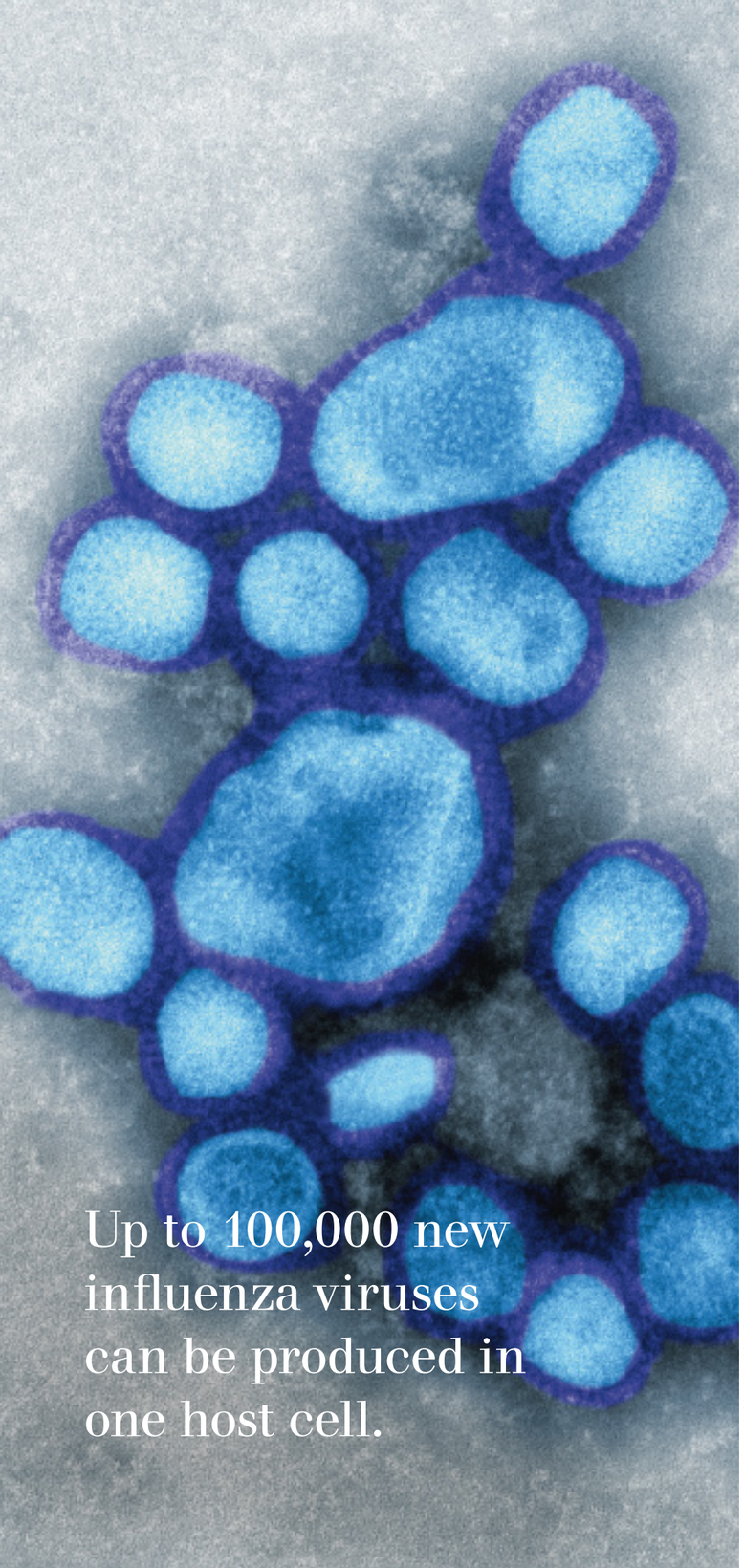
One could essentially consider each virus to be a temporary team made up of eight gene segments. The members are constantly being replaced, so that each year the teams are made up of a new group of players. The genes are recruited from an enormous reservoir of infected birds, and thousands of variants have already been discovered. The pathogens of the seasonal flu resemble those from preceding years. A portion of the population is therefore immune, and it is primarily children and the elderly who become sick. Sometimes, however, viral evolution leaps forward and produces a new strain.

The current definition used by the WHO, whose pandemic alert system comprises six phases, was drafted on the basis of experiences with the avian flu in 2005. This new virus strain was not very contagious, but it was frequently deadly. According to the WHO, a pandemic exists when a new virus strain is spreading throughout the entire population in various regions throughout the world. In late May, however, WHO Assistant Director General Keiji Fukada announced that this definition would be changed. A primary criterion in the future will be that a pandemic represents a significant hazard potential for humans. “We are trying to walk a fine line between not causing panic and not being complacent,” says Fukada.

Is this a repeat of 1918?

Fukada described the core of the problem very succinctly. A new virus strain can be identified very quickly today using >

ABSTRACT The WHO considers the “new flu” (Influenza A/H1N1) to be a pandemic, a worldwide threat. Precautionary planning helps to counter panic. Mathematical models support these measures, as do new methods of vaccine production. Protective measures in the workplace and at home can limit the risk of infection.



Up to 100,000 new influenza viruses can be produced in one host cell.

PHOTOGRAPHY: CORBIS, PICTURE-ALLIANCE/DPA

Barrels instead of ampoules: Barrels of the medicine Oseltamivir are stored in a secret location. This warehouse in the German state of North Rhine-Westphalia gives an impression of the quantities required.

> molecular diagnostics, but how dangerous it actually is cannot be reliably determined until much later. Only after many people have become ill can anything be said about the mortality rate. The virus could undergo further mutation at any time. And the "new flu" could already be dangerous for countries with inadequate health systems.

Planning helps avoid panic

There are a number of reasons why it is unlikely that the catastrophe of 1918 will be repeated, however. At that time, hundreds of thousands of malnourished people were crowded together in cramped conditions and under great stress in battlefield trenches and troop transports. "Those are ideal conditions for propagating an influenza virus," says Tim Brewer, who develops global health programs at McGill University in Montreal, Canada. Pre-existing conditions such as tuberculosis made many people back then particularly susceptible.

Many countries considered the disease a sign of weakness that had to be concealed from their wartime enemies. The pandemic became known as the "Spanish flu" because censorship of the press was less strict there and the King of Spain ultimately made his illness known to the public. Today international agreements allow the WHO to take a proactive role in many countries—either to gather information or to offer assistance. "There's much better coordination on the global level to respond to these kinds of episodes, if we compare the situation in 2009 with the SARS outbreaks of 2003, let alone with 1919," says Brewer.

Of course there is also a world of difference between the current state of medicine and that at the time of the Spanish flu. Nothing was known about influenza viruses in 1918. The most commonly used remedies to combat the disease were bloodletting, quinine derivatives, opium, and whiskey. Today physicians have antiviral medicines, vaccines, antibiotics, and ventilators at their disposal.

Yet the question remains: Will there be enough for everyone? The hospitals have prepared as best they can for a rush of patients. "We have prepared for the separate care of influenza patients and other patients," reports Susanne Huggett, who is forging plans at the Asklepios hospitals in Hamburg in the event of a pandemic. "We have stockpiled medicines, protective clothing, and disinfectants." It is particular important to protect hospital staff against infection. "We've been conducting training classes since 2006," says Huggett. "We want to avoid a panic by carefully explaining to our staff how they can protect themselves. Not even an FFP3 mask can help if you don't put it on properly."

A pandemic could result in the hospitals being confronted with a large number of patients requiring artificial ventilation. The Deutsche Gesellschaft für Pneumologie (German Society for Pneumonology) has long warned that intensive care units would not have sufficient capacity to meet the demand for artificial ventilation. The pneumonologists recommend that the hospitals make emergency use of simple ventilators such as those used for the in-home ventilation of people suffering from chronic lung diseases.

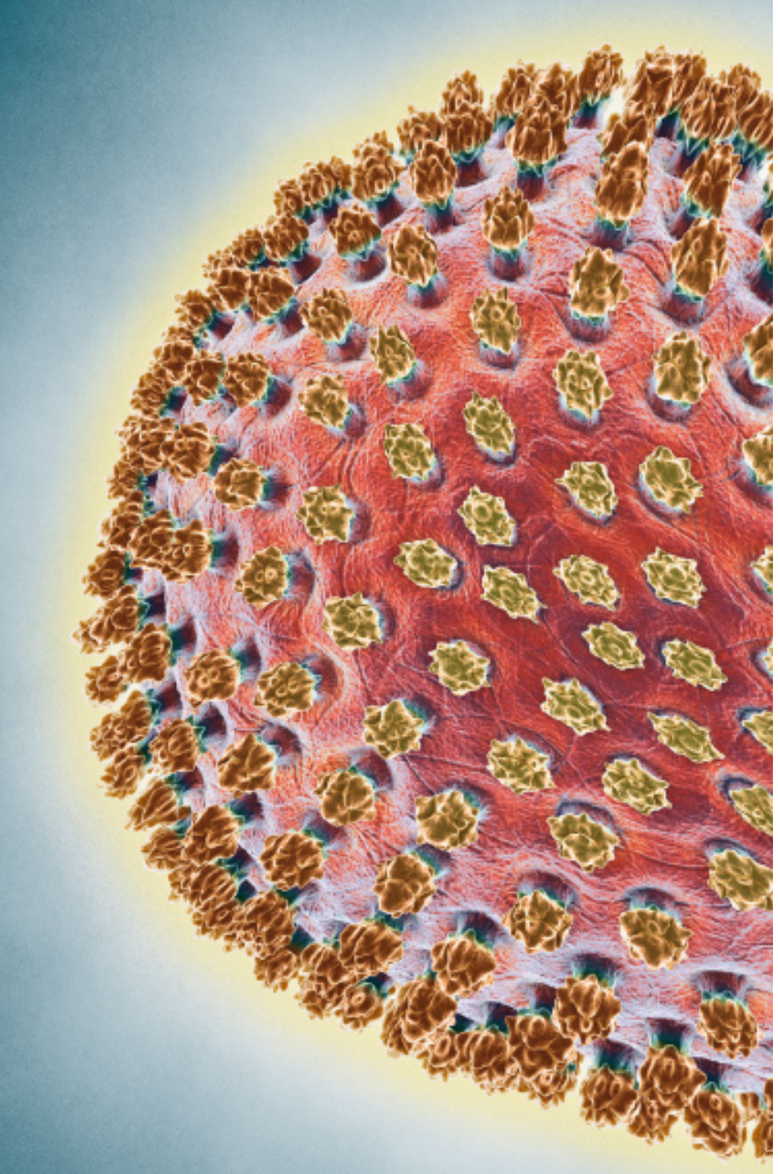
The U.S. states have stockpiled ventilators since this warning was issued. The expected requirements must be taken into consideration when choosing the devices, however. The units must be as inexpensive as possible, of course. They must be simple to use in mass deployment, and they must also remain functional in the event of a loss of the gas or power supply. "At the same time, it must be very easy to set the machine for the ventilation of the pulmonary patients to avoid damaging the lungs," explains Jan Evers, an intensive medicine product manager at Dräger. The Dräger device best meeting these requirements is the Savina, which supports invasive and non-invasive ventilation using ambient air. Even lighter and thus more mobile is the Carina non-invasive ventilator, which only offers limited monitoring, however. Another important consideration is that all gas-bearing parts can be replaced in order to avoid cross-infection.

Pandemics in the computer

To estimate the resources required in the event of a pandemic, scientists have been trying for years to simulate their probable course. "The critical factor here is the basic reproduction number (r_0)," says Markus Schwehm. He developed the simulation program "InfluSim"—which is now available online—at the University of Tübingen and founded a consulting firm. The r_0 indicates how many people on average will be infected by one sick person. If the number is greater than one, the virus will continue to spread and the infection will get out of control. The Spanish flu had a r_0 of approximately 2.5. „Initial estimations of r_0 were at 1.5," says Schwehm. The simulation suggests that in this case propagation can be stopped with relatively simple measures. According to Schwehm, these include hand hygiene and the general avoidance of contacts. The simulations have shown travel restrictions to have hardly any effects at all, since "there are far too many infections without symptoms."

Schwehm has some doubts about the low r_0. "I believe that it is actually 2.5, at which value we have no chance to stop the propagation." Just what course the pandemic will run also depends on another crucial factor that the pandemic researchers are carefully monitoring. How many of the infected persons develop any symptoms at all, and how many die? So far, Schwehm assumes that 75 percent of all people will eventually become infected with the "new flu." Many won't even notice anything, but will still be able to infect others. A quarter of the population would then get ill and exhibit serious symptoms; one in 200 persons would have to be hospitalized with complications, and 16 percent of these would probably die.

But it doesn't have to be this way. According to a telephone survey conducted in late May, six percent of the residents of New York reported having flu-like symptoms in the past few weeks. If this >



Glycoprotein “spikes” extend 10 to 14 nanometers above the surface of the virus.

PHOTOGRAPHY: CORBIS

> is the new pandemic, it would mean that it is running a much milder course than expected. “That would be good news,” says Schwehm, “because it would mean that the pandemic is already well advanced and will soon come to a stop. But I need better data before I change this parameter.”

There is one thing that Schwehm has not yet considered in his simulations: the development of vaccines. “First they said that the pandemic would be over before the vaccine could be developed,” he says. But that could change if the course of the pandemic is slowed and the vaccine is developed quickly. The Centers for Disease Control (CDC) in Atlanta, Georgia, U.S.A., distributed seed viruses to vaccine manufacturers throughout the world in May. These are now being inoculated into chicken eggs, where the vaccine is produced. Vaccinations against the “new flu” are scheduled to begin in Europe and the USA in fall 2009.

Vaccine from cell cultures

In past years a lot of money was invested to expand production capacities and to develop faster methods. One major pharmaceutical manufacturer is now producing a portion of the vaccine in cell cultures rather than chicken eggs. The regulatory approval processes for vaccines produced in this way are still more time-consuming, but the technology could prove to be the wave of the future. Despite the tremendous effort, vaccine production would bump up against its limits in the event of a pandemic. Global capacity lies between one and two billion doses of vaccine per year, with two vaccinations required for optimal immunization. It is thus clear that the vaccine supply falls far short of what is required to vaccinate everyone worldwide.

But the vaccination does not offer complete protection. It may well be that the “new virus” continues to be harmless and the seasonal flu is neglected in favor of the new vaccine. It is also possible that the virus will mutate, rendering the vaccine ineffective. The only way out of this dilemma is a universal influenza vaccine that is effective against all strains of the virus. A group at Harvard Medical School reported an initial breakthrough in animal trials in February 2009. The researchers produced antibodies that attack a genetically stable portion of the virus molecule.

The road from a breakthrough to a universal vaccine is a long one, so influenza viruses will probably still be around for many years to come. But remarkable progress has been made in the race against the virus. Never before has mankind been so well prepared. The nature of the viruses provides another reason for hope. It is not actually in the pathogen’s best interest if it kills its host and cannot spread any further. The mild course of the new pandemic so far could therefore mean that not just the humans, but also the viruses have learned in the course of their evolutionary progress. **Dr. Birgit Herden**

Further information online, including:
Checklist for companies
www.draeger.com/98/pandemic

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Can you plan a pandemic?

HARTMUT SCHMIDT, Strategic Marketing at Dräger, talks about the opportunities presented by careful planning.

What does a manufacturer of medical technology have to do in the event of an influenza pandemic?
We have to be in a position to react as quickly as possible. During the SARS epidemic and at the beginning of the “new flu,” for example, we delivered large numbers of ventilators and masks all over the world in the shortest time possible.

How are the needs of the customers changing?
A guaranteed ability to deliver needed equipment becomes increasingly important during a pandemic. Today there is also a greater demand for robust ventilators. If a major pandemic results in large numbers of patients needing to be treated in other hospital wards because the intensive care units are overfilled, there may not be an oxygen supply available, and there may not even be a reliable power supply. In such situations we would need ventilators that have an independent air supply and long-life batteries for the treatment of seriously ill patients. The ventilators also have to be easy to use, because in the event of an emergency they may have to be operated by laypersons following a doctor’s instructions.

Where do you see the greatest problems?
In the event of a global pandemic, the challenges will tend to be of a logistical nature rather than being due to a shortage of ventilators. We may be able to withstand the first wave of a pandemic, but if the supplies of medicines and protective equipment are used up and are not replenished before a (possible) second wave hits, things could get tight.

The greatest danger is that the infrastructure could begin to partially collapse. A quarter of the world’s population could be sick at the peak of a pandemic. This means that 25 percent of the truck drivers, ship captains, warehouse workers, etc. would not be available to work. An average supermarket only has food stocks that would last for 24 to 48 hours. It is conceivable that the power and water supplies could collapse. And in this environment we as a manufacturer would have to retain our ability to supply products—worldwide.

How can we prepare for this eventuality?
First, companies and private individuals should take the various protective measures to try to avoid infection as much as possible. Companies must review their supply chains and configure these to make them as robust as possible. This could mean having more than one supply channel, for example. Furthermore, planning scenarios should be used to rehearse which decisions have to be made in certain situations. Finally, you can’t really plan for a pandemic or any other catastrophe. You therefore have to have predefined management staffs, i.e. people who are trained and empowered to decide in the event of an emergency what needs to be done in each specific situation.

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