A SHELTER FROM THE PANDEMIC

Andrea Crisanti and Anna Meldolesi

BIG IDEAS

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BIG IDEAS

The SARS-CoV-2 virus took the world by surprise. While its spread across the world has exposed widespread organisational deficiencies in many countries, the pandemic has also shown the vitality of scientific research. To put this pandemic behind us and be ready for the next, we need to learn from our mistakes. One lesson is the critical importance of investing in scientific research. There are now many good vaccines available around the globe. Immunisation campaigns have proven their worth but we need to do much more.

Andrea Crisanti is a scientist working on innovative ways to control infectious diseases. He is known as the architect of the "Vo' experiment," which stopped all new infections in an Italian town near Venice that was at the centre of the country's outbreak. When SARS-CoV-2 began spreading, Crisanti was in the right place at the right time. He had just left Imperial College London to join the University of Padua in Italy, the European country most severely hit at the start of the pandemic.

The co-author, **Anna Meldolesi**, is a science journalist with the Italian daily Corriere della Sera. She has been following Crisanti's work in health policies for many years, even before COVID-19, when his main interest was malaria, an ancient and ever-present threat.

This is the seventeenth essay in the Big Ideas series created by the European Investment Bank. The series invites international thought leaders and experts to write about the most important issues of the day. These essays are a reminder that we need new thinking to protect the environment, promote equality and improve people's lives around the globe.

THE PACE OF DEVELOPMENTS IN THE COVID-19 PANDEMIC HAS BEEN DIZZYING. MANY GOVERNMENTS PUT CITIES INTO A LOCKDOWN.

THE COMPLEX TASK OF FLYING A PLANE WHILE BUILDING IT

For every complex problem, there is an answer that is clear, simple and wrong. Does this well-known line from the American writer H.L. Mencken apply to COVID-19? Does the new virus have a simple and correct answer? Or have we been searching in the wrong direction?

Since the beginning of 2020, when reports of an unusual pneumonia began spreading in China, a few lessons have been learned. We can now say that Mencken's motto is right in that there is no simple answer. There is no silver-bullet solution to the coronavirus crisis. We also know we made mistakes. Some approaches have proven better than others. If we could press the rewind button, many problems could have been avoided.

Some clues as to how we should tackle this crisis were already apparent in early spring 2020, but were not fully appreciated at the time. Properly interpreting these clues could have changed the course of the epidemic in Italy and across the world. For example, a key study was carried out between March and May 2020 in the village of Vo', near Padua in north-eastern Italy. This study, which we will come back to later in this essay, was among the first to shed light on the best ways to tackle the pandemic and stop the spread of the disease. It showed how contact tracing and population monitoring can deliver big results and keep many people safe. Unfortunately, this study was drowned out by the cacophony of information and opinions that accompanied the spread of COVID-19.

> **“If we could press the rewind button, many problems could have been avoided**

THE TWO-METRE RULE FOR SOCIAL DISTANCING IN ALL PREMISES OPEN TO THE PUBLIC AND WORKPLACES, WHERE REASONABLE.

Finding out what worked well and what should have been done differently are the keys to getting out of this pandemic and tackling other emerging pathogens. The SARS-CoV-2 virus showed us that we have been living in a society that has widespread organisational deficiencies.

We need new strategies of virus surveillance and contact tracing. We need to fight for better international coordination, which could include a reform of the World Health Organization. We need to pay greater attention to human interactions with other species and the protection of biodiversity. We need to be better prepared for future pandemics with improved data collection and analysis when an epidemic starts; and more institutional accountability and political leadership.

" Forgetting and hoping for the best are luxuries we can no longer afford

When this pandemic is over, many will want to forget about it. That is how we have dealt with previous epidemics but this would be a mistake. Forgetting and hoping for the best are luxuries we can no longer afford. The challenge ahead is not to get back to normal, to the ways things were, but to make the necessary changes, big and small that will protect us from similar events in the future.

Everything in the fight against the pandemic since early 2020 has felt rushed. When COVID-19 arrived, scientists and authorities had to apply emerging knowledge and rapidly integrate it into policies under extreme pressure. Discovering, preventing and treating all at once. Translating sound scientific research into updated protocols and evidence-based decisions requires solid training, wisdom, responsiveness and flexibility to understand both the big picture and the details. The scientific community, the World Health Organization and governments were found to be unprepared for this crisis. In February 2020, Italy was the

AS ITALY WAS DEALING WITH EUROPE'S WORST COVID-19 OUTBREAK, A MESSAGE OF HOPE, "EVERYTHING WILL BE ALL RIGHT", WENT VIRAL IN THE COUNTRY.

first European country to be hit by COVID-19. The viral storm was overwhelming for healthcare workers and researchers, policymakers and citizens.

Most developed countries have been lucky to have escaped rampant epidemics for decades. We have been protected because we had vaccines and drugs already on the market and because no serious diseases were spreading too widely, with the exception of HIV infections. While several new diseases, such as SARS-CoV (the coronavirus causing SARS) emerged during this time, these remained largely confined to the regions where they began without circulating in Europe and turning into a pandemic. The SARS-CoV-2 virus, however, rapidly spread everywhere. This required scientists from all over the world to divert their attention to researching, prototyping and manufacturing vaccines and treatments. It has been like flying a plane while building it.

" Most developed countries have been lucky to have escaped rampant epidemics for decades.

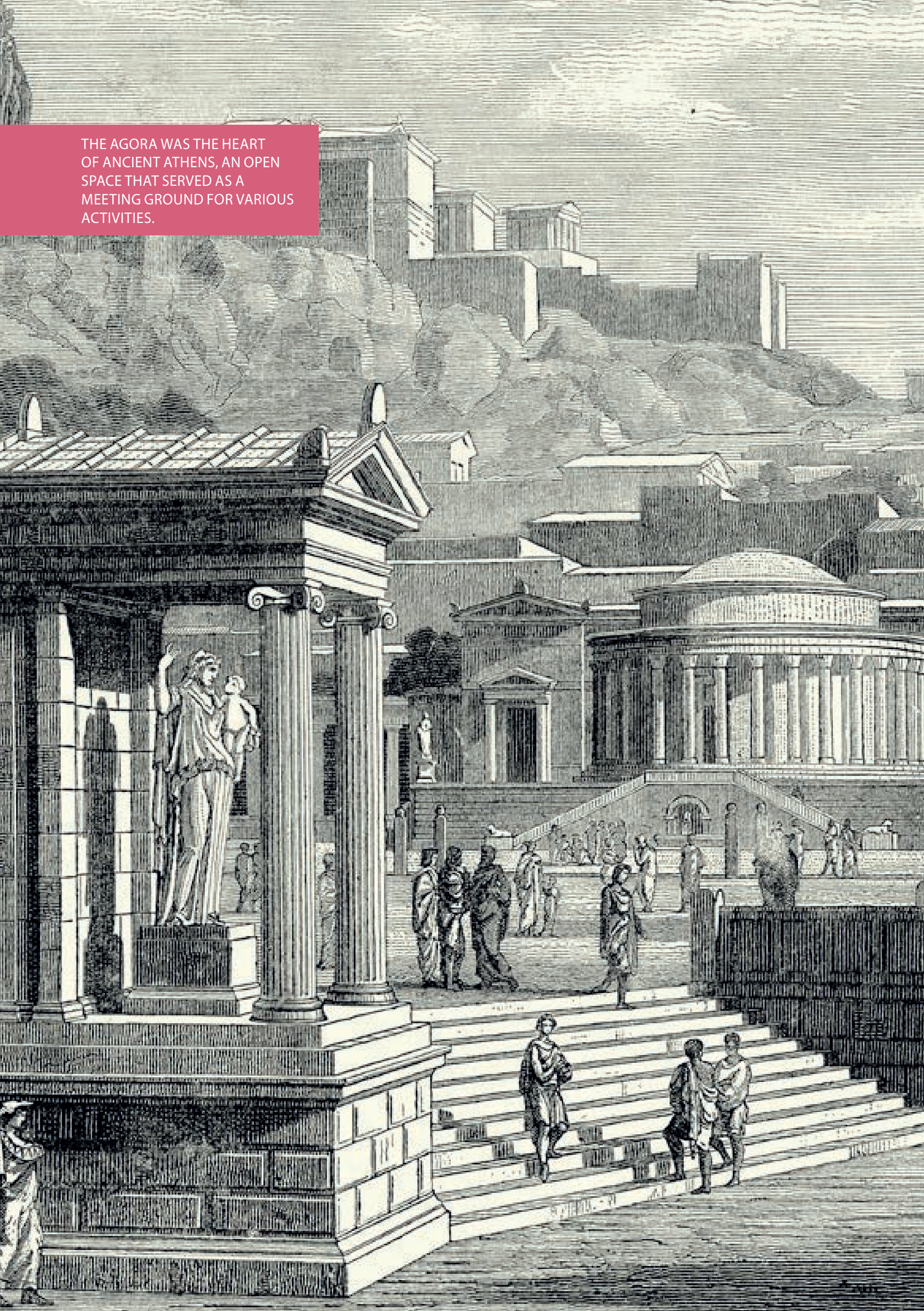
IN JANUARY 2020 PEOPLE IN WUHAN WERE PUT UNDER STRICT QUARANTINE, AND FACE MASKS AND SOCIAL DISTANCING BECAME MANDATORY.

THE HAMMER IN THE TOOLKIT

Comparing different epidemics is always a risky exercise. Pathogens behave differently depending on their biology, transmission routes and the structure of the societies in which they spread. Remedies made available by science and medicine are hugely uneven in terms of efficacy. In addition, the general context in which humans and germs interact has radically changed in the last few decades. Modern, global societies that move around often and quickly are easily exposed to viruses emerging on the other side of the globe. This makes humanity vulnerable. However, the flow of people and goods across borders is protected to some extent by scientific knowledge that can also travel at higher speeds worldwide today, and this is a significant advantage compared to the past.

Epidemics are a major force that cause historical change, just like wars, revolutions, and economic crises. We may struggle to imagine what the post COVID-19 world will look like. We will experience changes in employment, the economy, healthcare, research, international cooperation, competition, human interactions with the environment, and the lifestyle of future generations. It is hard to distinguish temporary effects from lasting ones. Historically, epidemics have often had long-term geopolitical impacts.

Ancient civilisations were aware of the threats posed by epidemics to society and established early warning criteria based on mathematical concepts. According to the Talmud, "A city that has fifteen hundred military age men such as Akko, and that suffers nine deaths in three days, is considered a plague. A city with five hundred such as Amiko and has three deaths in three days, that is considered a plague"[1]



THE AGORA WAS THE HEART OF ANCIENT ATHENS, AN OPEN SPACE THAT SERVED AS A MEETING GROUND FOR VARIOUS ACTIVITIES.

The Greek historian Thucydides was the first to describe an epidemic outbreak. The plague that broke out in 430 BC in Athens, which in fact was probably typhus, ravaged the Mediterranean and reached Greece through the port of Piraeus. It killed between 75 000 and 100 000 people in Athens, redefining the balance of power between Sparta and Athens[2]. The contagion emerges from Thucydides' account as a natural phenomenon exploiting practical, psychological and social vulnerabilities[3].

> **"The Greek historian Thucydides was the first to describe an epidemic outbreak.**

Infectious agents afflict societies through the specific conditions created by people in different places and times and reveal systemic weaknesses. Low standards of housing and sanitation, and the issue of individual needs versus community interests, were some of the critical factors thousands of years ago and still play a role today. However, the differences appear as marked as the similarities. According to Thucydides, in ancient Athens, "for the violence of the calamity was such that men, not knowing where to turn, grew reckless of all law, human and divine."

In the Middle Ages, the first great victory over a scary infectious disease, the plague, was not really the result of medical or scientific progress. Housing improvement and city planning together with ecological and climatic changes are thought to have played a role, reducing contact between humans and rats and lowering the efficiency of fleas and pathogenic bacteria.

THE BACTERIA THAT CAUSE PLAGUE — YERSINIA PESTIS — HAVE NEVER BEEN ERADICATED AND OCCASIONALLY RE-EMERGE FROM THEIR ANIMAL RESERVOIRS.

However, much credit goes to the adoption of a set of draconian measures establishing boards of health, mandatory burials, forced confinement of the sufferers, quarantine, and sanitary cordons around affected areas. Suffering was dramatic for sick people, imprisoned and abandoned, and for the outsiders scapegoated for spreading plague[4].

When the first measures began to take shape between the 12th and 13th centuries, the prevailing theory was that diseases were caused by lethal miasma rather than from person-to-person contagion. Therefore, anti-plague interventions were based on empirical observation instead of medical understanding. In particular, by impounding ships for 40 days and isolating their crew and passengers in the meantime, a crucial link in the chain of infectious transmission could be broken. Health authorities could not know, but 40 days were enough to ensure the death of fleas and pathogenic bacteria and exceeded the plague's incubation period. In practice, people who were healthy at the end of the quarantine were not contagious.

This approach was pioneered by the Republic of Venice and then imitated by other cities and countries, becoming more sophisticated and effective over time. With the consolidation of modern states, more military resources could be deployed and broader geographical areas could be controlled to stop microbial threats from land and sea. According to historians, political authorities acted in the dark, sometimes over-investing in useless and even counterproductive actions. Nevertheless, all things considered, the key measures worked well and the plague eventually disappeared from Europe in the eighteenth century as mysteriously as it had appeared. The bacteria that cause plague — Yersinia pestis — have never been eradicated and occasionally re-emerge from their animal reservoirs. Luckily, the disease is treatable with commonly available antibiotics, if caught soon enough.

LOCKING DOWN AFFECTED AREAS IS THE OLDEST TOOL IN THE POLICYMAKER'S TOOLKIT FOR INFECTIOUS DISEASES.

In brief, it is a fact that the pathogen that repeatedly devastated Europe for centuries was defeated by organising and militarily imposing public policies. Locking down affected areas is therefore the oldest tool in the policymaker's toolkit for infectious diseases. It works like a hammer to bring down the epidemic curve and it is still useful in the 21st century. Fortunately, modern epidemiology can offer better tools and greater benefits.

THE FIRST IMMUNISATION CAMPAIGNS KICKED OFF AT THE BEGINNING OF 2021.

VACCINES, THE GAME CHANGERS

Vaccines have proven the most cost-effective measure to control viruses and bacteria, as they provide protection and prevent outbreaks. However, there are also diseases, such as malaria, tuberculosis and HIV-AIDS for which an effective vaccine has never arrived, despite huge international efforts.

The global effort to develop COVID-19 vaccines in record time was a remarkable success. The three first vaccines were developed by Pfizer-BioNTech, Moderna and Oxford-AstraZeneca. The Pfizer-BioNTech and Moderna are mRNA vaccines which use a new approach. A messenger RNA is injected to teach our cells how to make a viral protein that triggers an immune response inside our bodies. The Pfizer and Moderna vaccines need to be stored at very cold temperatures and require at least two doses, which makes them difficult to deliver in some poor countries. The Oxford vaccine uses another harmless virus to carry into the body a genetic fragment coding for the same viral protein. It is one of the easiest to use as it can be stored in a fridge.

“Data transparency is crucial for people to trust in scientists, pharmaceutical companies, and institutions.

The first immunisation campaigns kicked off at the beginning of 2021. In Europe the vaccine rollout began relatively slowly and then gradually sped up as manufacturing capacity increased and stocks were fully deployed. Data transparency is crucial for people to trust in scientists, pharmaceutical companies, and institutions. Trust is, in turn, vital to achieve broad vaccination coverage. A global immunisation campaign like the one underway is unprecedented and involves complicated logistical coordination.

AS NEW VARIANTS EMERGE AND SPREAD, UNCERTAINTY MAY LEAD TO INCONSISTENCY.

Nor should the importance of correct communication be underestimated. It means explaining the importance of vaccination, preparing the media and the public for the occurrence of a small percentage of adverse events, clarifying that the arrival of vaccines does not mean the abandonment of other individual and collective protection measures such as wearing masks. The pandemic is a multidimensional challenge that requires timely action as well as vaccines, advanced therapies such as monoclonal antibodies, developed testing capacities and strategies and, last but not least, appropriate behavioural patterns.

We are lucky enough to have a range of options, including vaccines and candidate vaccines based on different technologies (messenger RNA, adenoviral vectors, protein subunits, etc.). To get the most from vaccination, we need to know to what extent the vaccines prevent people from getting sick or also from transmitting the virus, whether severe cases are prevented as well as those presenting few symptoms, how effectiveness varies in different age groups, and how long the immunity lasts. Breakthrough cases — infections in people who are fully vaccinated — are occurring.

As new variants emerge and spread, uncertainty may lead to inconsistency. The vaccines are showing some limits in terms of their ability to block transmission and in their duration of protection, highlighting the need to combine vaccination with effective safety measures.

OVERALL, THE DATA CONFIRM THAT IT IS POSSIBLE TO APPLY LIGHTER AND MORE LOCALISED RESTRICTIONS BY FOCUSING ON TIMELY AND ACTIVE SAFETY MEASURES EARLY ON.

COVID-19 STRATEGIES

Nobody knows how long COVID-19 will continue to be a public health emergency of international concern, how well the vaccination campaigns will keep pace with the virus evolution, or if SARS-CoV-2 will adapt to the human species over time, becoming milder as other human coronaviruses probably did centuries ago. Its predecessor, the SARS-CoV virus, seems to have disappeared entirely from circulation, but it never went pandemic. This is probably not the end of the story being written in the SARS-CoV-2 book.

> **"This is probably not the end of the story being written in the SARS-CoV-2 book.**

Hopefully, by the time COVID-19 loosens its grip, all countries will be better prepared against future threats. However, how should authorities respond to something like a hypothetical SARS-CoV-3 when it emerges? As the pandemic has progressed, scientists have been able to study and compare the effects of different sets of policies on the spread of the disease. Overall, the data confirm that it is possible to apply lighter and more localised restrictions by focusing on timely and active safety measures early on.

When the system is well organised and prepared to react, transmission chains may be broken by monitoring the groups more likely to be infected and testing the people who meet positive cases. By preventing and promptly extinguishing new outbreaks in this way, many lives could be saved without overly encroaching on people's constitutional rights or unnecessarily damaging the economy. It must be recognised, however, that a nuanced approach requires careful planning and effective cooperation between central and local authorities. During the second wave, Italy, for example, was divided into red, orange and yellow regions, according to 21 parameters, but the result was far from satisfying.

SWEDEN MADE SOCIAL DISTANCING A MATTER OF SELF-REGULATION.

In managing the current pandemic, two main containment strategies have been applied by governments with variations reflecting local contexts and capacities. The traditional approach is based on restricting all citizens' movement in a more or less severe way. Italy is the European country that in winter-spring 2020 came closest to the Chinese model in terms of the severity of its lockdown. At the opposite end of the spectrum is Sweden, which left almost total freedom to its citizens in the framework of voluntary social distancing. Alternatively, a more innovative strategy has emerged in places such as South Korea, Singapore and Taiwan, based on active surveillance of the problem. This approach focuses on isolating positive cases, tracing their contacts, and extending the use of tests to asymptomatic contacts to block the virus's silent transmission.

IN JUNE 2020 ITALIANS WERE HOPING THAT THE VIRUS WAS GONE.

GOING VIRAL IS NOT GOOD

Contact tracing is impossible to carry out when the virus is widespread. The number of daily infections depends on three factors: the ability of the virus to transmit itself efficiently from one person to another, collective behaviour, and the ability of the healthcare system to effectively identify and isolate healthy and sick carriers. Depending on the ability of the healthcare system to identify and isolate outbreaks, as well as on collective behaviour, a sort of precarious balance is created with the virus that determines the number of people who become infected each day.

Understanding this dynamic is key to keep this number as low as possible, protecting vulnerable people and avoiding the collapse of the healthcare system and therefore the explosion of serious cases and increased mortality. If you change collective behaviour, by for example reopening schools or economic sectors without adjusting the capacity of the health and safety surveillance system, you reach the breakdown threshold. When the number of cases exceeds the tracking capacity of the healthcare system, the only option available remains lockdown, an extreme choice given the economic consequences.

> **"Contact tracing is impossible to carry out when the virus is widespread.**

Containment measures can be a useful tool but their effect will be only temporary if, at the same time, countries do not invest in national surveillance plans to consolidate the progress and break the spiral. In Italy, for example, there were only a handful of cases per day in June 2020, and Italians were hoping that the virus was gone. However, behaviours that favour the transmission and spread of the virus throughout the country resumed and by the end of

OUTDOOR SUMMER SCHOOL ACTIVITIES IN TURIN, ITALY, WITH SOCIAL DISTANCING MEASURES.

August 2020, contagions began to increase by the day, but this warning signal was ignored.

Italy reopened its schools and resumed economic life without having invested enough resources, IT tools and logistics in an active surveillance system capable of interrupting the transmission chains and consolidating the results obtained with huge human and economic sacrifices. In a few weeks, the dynamics of contagion went exponential. Italy battled a second wave in September 2020 and then a third wave in April 2021, with all its regions in the "red zone" - the highest tier of restrictions. At the time of writing, Italy has registered more deaths than many EU countries combined with a high mortality rate per 100 000 inhabitants.

TESTING AT SCALE DURING THE COVID-19 PANDEMIC HAS SAVED LIVES.

NETWORK TESTING

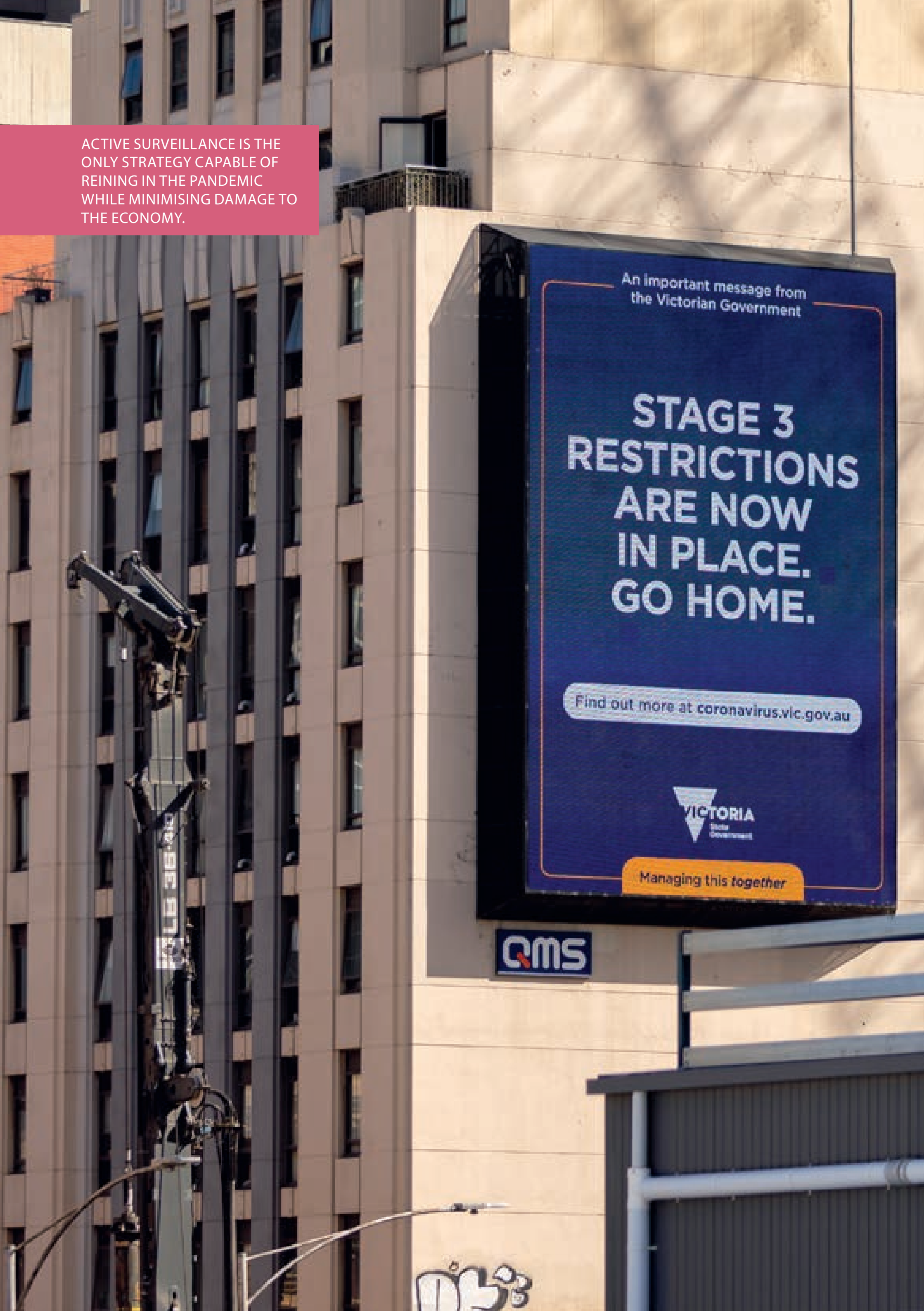
Starting with an infected person, those who transmitted the infection to him or her are in the vast majority of cases in their circle of friends, work colleagues, relatives or neighbours. In this space of interactions, you will also find contacts who have themselves been infected. If all these people are tested for the virus and the positives are isolated and treated, the transmission chain is interrupted.

This "network testing" approach requires the ability to do a large number of molecular tests, logistics to make them accessible in a timely manner where they are needed, and IT support to monitor the dynamics of transmission and the situations that promote their growth. It is worth noting that network testing has logistic and cost-effectiveness advantages over contact tracing because you already know that relatives, colleagues, and neighbours of positive cases are at risk; you do not need location data from mobile phones or credit cards to trace them.

"If all these people are tested for the virus and the positives are isolated and treated, the transmission chain is interrupted.

The Veneto region pursued this strategy in Italy during the first epidemic wave, obtaining excellent results. Comparing epidemic trends in Veneto and the neighbouring Lombardy region is a complex task because of their structural differences (decentralisation of the regional health system, public-private mix in healthcare and more). However, several indicators, such as the percentage of infected subjects requiring intensive care and the death toll in Veneto versus Lombardy, strongly suggest that the timely application of active surveillance principles does save lives.

ACTIVE SURVEILLANCE IS THE ONLY STRATEGY CAPABLE OF REINING IN THE PANDEMIC WHILE MINIMISING DAMAGE TO THE ECONOMY.



Furthermore, active surveillance is the only strategy capable of reining in the pandemic while minimising damage to the economy and maintaining essential activities such as schools. It is worth stressing that safeguarding economic stability and educational continuity is a way to indirectly improve people's health and quality of future life. In general, it seems that the countries that did best during the first pandemic wave have something in common: a well-established public health system and a recent encounter with other epidemics. Combining the two, we have Japan, South Korea, Taiwan, Singapore, Australia and New Zealand standing out.

ACCORDING TO A WITTY DESCRIPTION BY THE BIOLOGISTS JEAN AND PETER MEDAWAR IN 1977, A VIRUS IS "A PIECE OF BAD NEWS WRAPPED UP IN PROTEIN".

KNOW YOUR ENEMY

Slowing down the spread of an emerging pathogen buys time to strengthen assistance and care facilities in the area. It is time that virologists, immunologists and geneticists can also put to good use, studying how the microorganism behaves, how the human immune system reacts, which factors make people more or less vulnerable to the disease.

According to a witty description by the biologists Jean and Peter Medawar in 1977, a virus is "a piece of bad news wrapped up in protein". When a virus infects a cell, it hijacks the cellular machinery, forcing the host to meet the invader's demands.
Genetic instructions are organised in paragraphs (the genes), and altogether they make up the genome.

"When a virus infects a cell, it hijacks the cellular machinery, forcing the host to meet the invader's demands.

The SARS-CoV-2 genome is a string of nearly 30 000 letters; in comparison, the human genome is over 3 billion. It encodes for some 30 proteins needed to carry out a range of tasks whose final goal is to turn human cells into factories that churn out countless viral particles ready to infect further cells. They serve as structural components, tools to replicate and assemble, tricks to camouflage the virus and suppress immune responses and more. Spike proteins are particularly iconic, as they form the crown-like structures that give coronaviruses their name. These protrusions on the virus's surface can pick the lock on the door of human cells (ACE2 receptors), leading to infection. SARS-CoV-2 prefers human airways, but can attack many organs. Intervening on key-lock mechanisms through drugs or vaccines could be a promising way to sabotage the virus's entry into the body.

ACCORDING TO SOME RESEARCHERS, THE COVID-19 PANDEMIC BEGAN WHEN ANIMALS AT THE HUANAN MARKET IN WUHAN, CHINA, PASSED THE VIRUS ON TO PEOPLE.

Sequencing the viral genome is square one in modern virology. It means reading the instruction manual for the infectious agent, comparing its structure with similar viruses, and interpreting the messages encoded in an effort to spot any weak points. The genome can also be read as a compendium of an organism's evolutionary history. Sequence similarities with viruses infecting other animal species may suggest a common point of origin. This is how a group of Chinese researchers came to believe that SARS-CoV-2 is the mutated variant of a strain that routinely infects bats. The germ could have jumped to humans directly, following contact between an infected bat and a human venturing into its wild habitat. However, it cannot be ruled out that a third type of animal may have acted as an intermediate host, facilitating the transmission. In the past, using the same kind of reasoning, scientists tried to identify the animal reservoir of another coronavirus, SARS-CoV. In this case, the cross-species chain was probably from bats to civets to humans.

"Sequencing the viral genome is square one in modern virology.

The genome also provides the information necessary to reject the conspiracy theory that SARS-CoV-2 was engineered in a Chinese lab by inserting fragments from different viruses. A geneticist's trained eye can spot transgenes when present, just like an art expert can distinguish a real antique from a fake. To date, all the available evidence points to the conclusion that this virus is a natural product of biological evolution. The first published sequence comes from the first known outbreak and involves the SARS-CoV-2 strain that infected a worker in Wuhan's wildlife market. Then, as the virus was isolated in other patients and new locations in China and worldwide, including Italy, thousands of sequences were added to public databases and made available to the international scientific community.

IMMUNISATION IS KEY.
THE LESS THE VIRUS REPLICATES,
THE FEWER VARIANTS DEVELOP.

All these genomic data are useful because, every time the virus replicates in a host cell, a few mutations creep into the genome. Most of the time, these are minor variations with no relevant effects. But with mutation after mutation, SARS-CoV-2 could change enough to become more or less aggressive, more or less contagious, more or less selective in choosing its victims. All viruses mutate; when mutations accumulate and give the virus new characteristics "variants" emerge. To prevent this, the only way is immunisation: the less the virus replicates, the fewer variants develop. This is where the spread of infection stops.

THE OMICRON VARIANT HAS AN R0 SIMILAR TO THAT OF DELTA BUT HAS SPREAD FASTER THAN DELTA.

WHEN A VIRUS MUTATES

A vast number of genetic variants of the SARS-CoV-2 are continuously generated as a function of virus multiplication upon transmission from person to person. These variants differ in terms of fitness, measured as the ability to spread in a population of susceptible hosts. Before the introduction of mass vaccination, genetic variants with increased infectivity (R0) progressively outcompeted other variants. The Delta variant — which has an R0 between 7-9 comparable to that of chickenpox — has become prevalent worldwide to reach in most places a frequency of 99% of all viruses sequenced. However, the introduction of vaccination has changed the ecological landscape offering variants with the ability to infect vaccinated individuals the opportunity to spread at the expense of the Delta variant even if they have a lower R0. The Omicron variant has an R0 similar to that of Delta but has spread faster than Delta in European countries as it can efficiently infect people that have completed the two doses vaccination regimen.

> **“The more sequences we have, the better we can trace the virus’s transmission chains and migration routes**

The events that have changed the world are written in the code of life and geneticists are deciphering the whole story with the help of bioinformatics. The more sequences we have, the better we can trace the virus’s transmission chains and migration routes, following the Ariadne’s thread of genomics in the pandemic labyrinth. Using this kind of comparative analysis gives you a molecular clock, which marks the fatal jump into humans in November 2019. Rumours about mysterious pneumonia cases in the Chinese city of Wuhan surfaced for the first time at the end of December that year.

VIRUSES ARE THE SMALLEST INFECTIOUS AGENTS THAT ATTACK HUMANS.

The first practical application of sequencing, however, is diagnostics. The viral genome is the identikit on which molecular tests such as swabs are based. It provides the genetic profile to search the samples taken from suspected cases, diagnose the infection, and then demonstrate recovery.

Viruses are the smallest infectious agents that attack humans, but the coronavirus family members are relatively large compared to many other viruses. SARS-CoV-2 measures 125 nanometres, with a nanometre being one billionth of a metre. Although small compared to higher organisms, the SARS-CoV-2 genome of 30 000 letters is large for a virus. Its genetic manual is more than twice as long as that of flu and more than three times the length of HIV's.
SARS-CoV-2 is an RNA virus, meaning that it differs from most germs and all higher organisms because its genetic material is ribonucleic acid rather than deoxyribonucleic acid (DNA). RNA viruses generally incorporate mutations at a faster pace than DNA viruses, but coronaviruses are peculiar due to their replication process's faithfulness. Indeed, they have a proofreading mechanism that is useful to partially fix the typos when the genome is copied inside the host cell.

"The viral genome is the identikit on which molecular tests such as swabs are based.

As a result, coronaviruses have a mutation rate three times lower than influenza. This genetic stability is good news because setting up a vaccine for a fast-mutating virus is more complicated. Coronaviruses, however, are quite promiscuous and dynamic: the strains that generally infect dogs, for example, can attack cats, those of cats can harm pigs. When two different coronaviruses are found within the same host cell, they can exchange genetic fragments generating

TWO DIFFERENT CORONAVIRUSES IN THE SAME HOST CELL CAN EXCHANGE GENETIC NEW VARIANTS THAT CAN INFECT OTHER TYPES OF CELLS AND ORGANISMS.

new variants that can infect other types of cells and organisms. This process is called recombination, it often occurs in bats, and it is one of the tricks used by coronaviruses to evolve.

The coronavirus family has dozens of strains or types, of which at least seven can infect humans. Four strains cause the common cold and are relatively harmless. Two are more aggressive and cause severe respiratory syndromes similar to COVID-19. The first is SARS, which in 2003 spread from China to other Asian countries and Canada. The other is called MERS and appeared for the first time in the Middle East in 2012. Being close relatives, they resemble each other and have similar evolutionary histories. However, their differences are relevant as well. Compared to SARS-CoV and MERS-CoV, SARS-Cov-2 is less lethal but more transmissible. The first two viruses almost exclusively attack the lower respiratory tract, while SARS-CoV-2 penetrates both the lungs and the upper airways. In comparison with its older cousins, it is even more contagious in the absence of symptoms, which is one of the main reasons it spread so rapidly worldwide.

“The coronavirus family has dozens of strains or types, of which at least seven can infect humans.

Coronavirus experts think that SARS-CoV-2 may have hidden out in nature for decades before jumping into people and starting a pandemic. Therefore, it cannot be ruled out that other potentially dangerous members of the coronavirus family are ready to emerge from wild animals if their ecological niche is disturbed. As exceptional as the current situation may seem, there is no doubt that the lessons we are learning now will be useful again in the future. What can we do better next time?

IN VO' ONLY PEOPLE WHO TESTED POSITIVE WERE TOLD TO STAY AT HOME.

THE VILLAGE AND THE WORLD OUTSIDE

To understand how a modern epidemiological approach should work, it is useful to come back to Vo'. This village near Padua was unlucky enough to mourn the first Italian victim of COVID-19 but also lucky to become the first documented example of outbreak suppression. Vo' became the theatre of an ideal epidemiological experiment when local authorities decided to isolate the village for two weeks soon after the first death was registered on 21 February 2020. Almost all the 3 300 inhabitants were swabbed twice, at the beginning and at the end of the isolation period.

> **"If you want to eliminate a cluster, you have to lock down the village or neighbourhood, test everybody, and isolate the positives.**

The evidence collected in Vo' in the February-March 2020 double survey is eye opening because it's an unbiased dataset, including all ages and social categories. It is much more representative than the cohorts tested in other studies around the world, such as military or cruise ships, homeless shelters, or nursing homes. The epidemiological picture taken in Vo' is representative also because the inhabitants continued to live almost as usual during their two-week lockdown, forbidden to leave the village but free to move inside its boundaries. Only people who tested positive were told to stay at home. If you want to eliminate a cluster, you have to lock down the village or neighbourhood, test everybody, and isolate the positives.

This is a realistic yet simple representation of an outbreak, much more intelligible for researchers than a big town where the network of contacts is a tangled mess. Therefore, what was done in Vo' could not have been carried out in Milan, for example. However, what we found out in Vo' is valid in most places. The first message from this

THE MOST SURPRISING RESULT OF THE VO' STUDY WAS THE HIGH RATE OF ASYMPTOMATIC CASES.

study is that children were not infected easily and that primary schools were therefore a less risky environment than high schools. Indeed, no infections were detected in the 234 children tested whose ages ranged from zero to ten, even among those living in the same household as infected individuals. The most surprising result, however, was the high rate of asymptomatic cases. Over 40% of the confirmed SARS-CoV-2 infections detected across the two surveys did not have symptoms at the time of swab testing and did not develop symptoms afterwards.

In brief, if you have a certain number of symptomatic individuals, there likely are as many with few or no symptoms who are unknowingly carrying the virus around. If they had not been promptly identified and isolated in Vo', the outbreak would have spread like wildfire, the way it did in several villages in neighbouring Lombardy. Silent transmission is the real superpower of this virus. The efficiency of the outbreak suppression carried out in Vo' by network testing clearly demonstrates what active surveillance can do when started early.

"Silent transmission is the real superpower of this virus.

The first two rounds of testing made it possible to capture a dynamic picture of the epidemic when the threat was still underestimated by many, between February and March. The study then continued in May, testing the inhabitants' antibody response, which revealed further details about the virus's silent spread before the first death. The third part of the project also investigated the human genome of the population and the positive swabs' viral genome. These data should help understand why some people are fine despite having contracted the infection, while the unluckiest ones succumb, need hospitalisation, or intensive care.

TESTING STRATEGIES MUST BE SMART AND WELL THOUGHT THROUGH.

The Vo' case study inspired the policies of the neighbouring town of Padua and, to a lesser extent, the whole Veneto region's strategy during the winter and spring of 2020. After collection, samples typically need to be transported to a centralised laboratory managed by experienced staff, which increases the costs, lowers the frequency, and delays the results, limiting the impact of the surveillance strategy. The keys to success in Padua were the purchase of "next-generation" polymerase chain reaction (PCR) devices (a laboratory apparatus which amplifies segments of DNA), the in-house production of reagents in short supply, and above all, the vision that when you are in emergency conditions, prevention is not a luxury but a strategic investment and a necessity.

"Watching the pandemic evolve from the Vo' observatory, it seems plain enough that most countries would benefit from revised pandemic plans

Watching the pandemic evolve from the Vo' observatory, it seems plain enough that most countries would benefit from revised pandemic plans, with emphasis added to the section on preparedness for active surveillance. Stockpiling devices and reagents is not sufficient; you must hire and train the test-and-trace staff, and be prepared to immediately start the process by mobilising people and things where the outbreaks occur. Testing strategies must be smart. They should carefully consider who needs to be tested and which tests should be used. Testing strategies may need to evolve along with the development of the pandemic to avoid bottlenecks and to make the best use of technological advancements in diagnostics. Fast, simple, and portable tests already exist and can be put to good use, but are not reliable enough to completely replace classic molecular tests. Point-of-care tests meeting the gold standard of PCR in centralised labs, however, would be transformative.

TOTAL VICTORIES OVER DISEASES ARE THE EXCEPTION RATHER THAN THE RULE.

GETTING BACK TO NORMAL IS NOT ENOUGH

Since the 1970s, many have cherished the dream of erasing all major infectious diseases, but this goal has proved illusive. Indeed, according to the Yale historian Frank Snowden, this illusion led developed countries to a "unilateral and premature disarmament" in the struggle between humans and germs, shifting funds and brains towards other health issues. Total victories over diseases are the exception rather than the rule. Smallpox has been eradicated and polio has almost been extinguished but our future is not a germ-free Eden. Instead, it looks like a Sisyphean effort. Medicine, nutrition, and sanitation have lengthened the average lifespan; thus, a high proportion of the population reaches an advanced age living with a weak immune system. Hospitals and nursing homes risk becoming infection hotspots, without due care, with the worst-case scenario of evolving drug-resistant germs. COVID-19 could remain with us for a while and even become endemic.

"COVID-19 could remain with us for a while and even become endemic.

Darwinian evolution is a never-ending story and the biosphere is a complex network of relationships. The human species can be attacked by thousands of viruses and bacteria. Many of these germs replicate and mutate at a furious pace. The challenge is made more difficult by the emergence of new diseases and the comeback of old foes. Over the past 50 years, humanity has had to face over 40 new pathogens, including: SARS and its cousin MERS, but also HIV, Ebola and its cousin Marburg, and then Nipah, Hantavirus, Lassa fever, Legionnaires' disease, Hepatitis C, Lyme disease, Rift Valley fever, West Nile virus, Bovine Spongiform Encephalopathy, Chikungunya, Norovirus, H5N1 (avian flu), and Zika.

NOW IT IS TIME TO LEARN FROM SARS-COV-2 HOW TO DEFEND HUMANITY FROM FUTURE MICROBIAL THREATS.

According to the World Health Organization, as many as 1 100 epidemic events occurred in the world between 2002 and 2007. The H1N1 pandemic influenza, also called swine flu, surprised us in 2009. It was a warning call, but the world reverted to business as usual too soon and SARS-CoV-2 caught us unprepared. Now it is time to learn from SARS-CoV-2 how to defend humanity from future microbial threats, because experts agree they will come. It is not a question of if but of when. COVID-19 is suited to our time and we can argue it is not a random event. If this disease has spread globally, it is because it is a perfect fit for 21st-century societies. A respiratory virus can travel from Beijing to Milan or New York in a matter of hours.

The planet has nearly 8 billion inhabitants and the rush to exploit natural resources leads to the invasion of remote habitats, bringing humans into contact with wild populations and their pathogens. Bats can move close to villages when a forest is destroyed, as probably happened in West Africa with the Ebola outbreak of 2014-2016. Alternatively, hunters can get into secluded caves looking for preys to sell at wildlife markets, like the one suspected at the beginning of the SARS-CoV-2 epidemic in Wuhan. Transmission from animals to humans often stops shortly after the inter-species jump because the virus does not pass efficiently from person to person. Unfortunately, however, it does sometimes continue. If it is contagious enough, it can bring national healthcare systems to their knees, even in rich countries.

“A respiratory virus can travel from Beijing to Milan or New York in a matter of hours.

A GENEROUS DOSE OF LUCK IS REQUIRED, BUT IT IS NOT ENOUGH.

Citizens deserve to be trusted: if correctly informed by competent and transparent authorities, they mostly do the right thing. National health systems work best when they are public, tightly connected to local communities and well-funded. Good scientific research must be supported before emergencies happen. A generous dose of luck is required, but it is not enough. There must be funds, organisation, perseverance, and strategic thinking. It is complex for sure, but clearly what needs to be done.

NOTES

[1] Babylonian Talmud, Tractate Taanit, 21A.

[2] https://pubmed.ncbi.nlm.nih.gov/19787658/#:~:text=In%20430%20BC%2C%20a%20plague,of%20the%20city's%20population%2C%20died

[3] Thucydides, The Peloponnesian War (2009)

[4] Frank Snowden, Epidemics and society. From the Black Death to the Present (2019)

BIOGRAPHIES

Andrea Crisanti is Director of the Department of Molecular Medicine and of the Laboratory of Virology and Microbiology at the Hospital/ University of Padua, Italy. He recently returned to Italy from Imperial College London, where he is professor of molecular parasitology. He has pioneered the molecular biology of the human malaria vector Anopheles gambiae and has made several important scientific contributions that advanced the genetic and molecular knowledge of the malaria parasite and its mosquito vector.

His work is based on a visionary solution designed to harness genetic elements similar to yeast homing endonuclease genes that would allow genetic modifications to spread from a few individuals to an entire vector population.

The power of this approach was recently demonstrated by the crashing of laboratory cage populations inoculated with a relatively small number of individuals carrying a gene drive construct that targeted a conserved and constrained sequence in a female-specific region of a gene called doublesex. This so-called gene drive has important implications beyond malaria, for the control of other vector-borne diseases, of agricultural pests threatening our food security, and of invasive species in fragile ecosystems.

More recently, with the pilot study of Vo' Euganeo, Professor Crisanti has provided key insights into COVID epidemiology that have informed virus control measures both nationally and in other countries, and has been recognised for his involvement in a dedicated high-calibre task force for the management of the COVID-19 emergency in Veneto.

Anna Meldolesi is a science journalist and writer with a degree in Biological Sciences from the University of Bologna and a Master in Science Communication from the International School for Advanced Studies in Trieste (Sissa). She teaches science journalism in the Master of Multimedia Journalism degree course of the IULM University in Milan. Her latest book concerns the genome editing revolution ("E l'uomo creò l'uomo. CRISPR e la rivoluzione dell'editing genomico", Bollati Boringhieri, updated edition, 2021) and she runs a bilingual blog on the same topics called CRISPeR Frenzy (https://mycrispr.blog/).

Her previous books cover a wide range of subjects including human evolution, agricultural biotechnology, prenatal sex selection, and psychology. She writes for the leading Italian newspaper Corriere della Sera and the Italian edition of Scientific American. She was co-founder and editor-at-large of the science magazine "darwin". From 2000 to 2013 she covered Italian news for Nature Biotechnology. She is a member of the scientific committee of the Festival della Scienza held in Genoa and frequently appears as a speaker at other public events.

Her work has won several awards including the Eugenio Aringhieri Special Prize; the Galileo Literary Award silver medal; the Premio Anima for Social Values; the Capo D'Orlando Prize for Science Communication; and the Marino Golinelli European Award for Journalism in Genetics.

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