Imperial College London

THE FORUM

The future of vaccination

Vaccines are one of the greatest triumphs in modern medicine, saving up to 3m lives each year. They are widely regarded as the single most cost-effective public health intervention: every dollar spent on childhood immunisations in Africa returns $44 in economic benefits.

We mostly think of vaccines as a way of protecting against communicable (infectious) childhood diseases such as measles. In fact, vaccines are far more versatile. They offer hope for combating HIV as well as non-communicable diseases such as cancer and Alzheimer's disease, due in part to the development of DNA and RNA vaccination techniques.

Fast-tracked vaccines have the potential to contain disease outbreaks before they escalate into epidemics or pandemics. Vaccines can also target antimicrobial resistance (AMR), a growing threat that jeopardises hard-won gains in public health and could claim as many as 10m lives annually by 2050.

This feature offers a broad overview on vaccines, covering the following five areas:

- what is a vaccine and how does it work?
- the global picture on vaccination today
- barriers to vaccination – poverty, transport, storage and public trust
- diseases targeted by vaccines in development
- building the infrastructure required to fast-track the research and manufacture of new vaccines

While the feature paints a worldwide picture, it highlights the role that the UK, and British universities such as Imperial, can play as global innovators. In truth, global and domestic agendas overlap: infectious diseases erupting in distant parts of the world have the potential to cross borders. The outbreaks of Ebola in 2014–2016, Zika in 2015 and ongoing avian influenza episodes, such as H5N1 or 'bird flu', have exposed deficiencies in global preparedness against both existing and emerging biological threats.

Tackling global health issues is as much a strategy of enlightened self-interest as of altruism. It is no surprise, therefore, that Imperial academics have presented their vaccine research work to the World Economic Forum in Davos.

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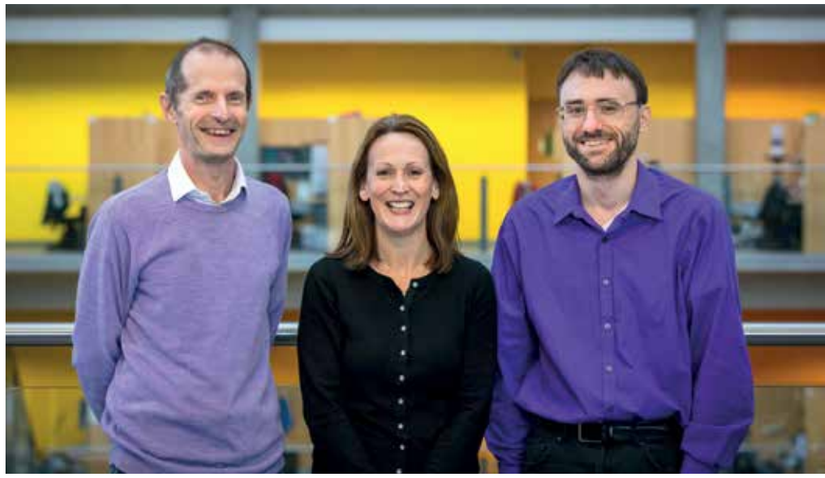

Professor Robin Shattock, Professor Wendy Barclay and Professor Jason Hallett presented their research to the World Economic Forum in Davos.

Such research offers the opportunity to innovate in science and manufacturing; to save lives; enhance wellbeing; and even to safeguard the future of humanity.

The feature includes interviews with academics in the cross-disciplinary Imperial Network for Vaccine Research, and other researchers and policymakers. These interviews focus on future vaccine research and the policy changes needed to maximise the benefits of that research.

Some key worldwide and UK statistics:

- A record 116m children were vaccinated globally in 2017, representing a coverage of 85 per cent.
- Vaccination is estimated to save 2–3m lives annually; a further 1.5m deaths could be prevented through better coverage.
- The Merck v920 vaccine against Ebola, developed in response to the 2014–2016 West Africa outbreak, is credited with saving lives in the ongoing (and now second-largest) outbreak in the Democratic Republic of Congo.
- Since 2010, 113 countries have introduced new vaccines, such as the human papilloma virus (HPV) vaccine.
- UNICEF reports that, in 2018, the number of measles cases rose in 98 countries

What is a vaccine and how does it work?

The World Health Organisation defines a vaccine as “a biological preparation that improves immunity to a particular disease”. It is usually made up of an attenuated (weakened) or inactivated form of a disease-causing microorganism (alternatively, it can be a surface protein or an adapted form of a toxin produced by the microorganism). When a vaccine is administered – orally, by injection or nasal spray – it stimulates the production of antibodies by the immune system. The antibodies recognise the ‘foreign’ invader and mount an attack.

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The principle of vaccination dates back to the 18th century, when British doctor Edward Jenner observed that milkmaids, who were exposed to cowpox, seemed immune to the related but potentially fatal disease of smallpox, which had a mortality rate of between 20 and 60 per cent. He even coined the term vaccination: *vacca* is the Latin for cow. In 1980, smallpox became the first disease to be eradicated through vaccination.

What is the global picture on vaccination today?

There are 26 available vaccines listed by the WHO, covering a range of preventable diseases such as dengue, cholera, measles, mumps, rubella, polio, hepatitis A, tetanus and rotavirus. Most countries have a schedule for vaccinations throughout the life course. **Six are offered to adults free by the NHS**.

The WHO sets a target that 95 per cent of children are immunised against vaccine-preventable diseases. Reaching this confers ‘herd immunity’: it stops diseases circulating, offering protection to those who cannot be vaccinated because of allergies, immune disorders or other illnesses. The **UK falls short of the 95 per cent target** with the measles/mumps/rubella (MMR) vaccine. Measles cases have resurfaced in the UK and in other countries. More distressingly around the world an estimated 1.5m deaths could be prevented if current vaccines were used more widely.

“We need to help manufacturers in low and middle income countries make vaccines more efficiently and at lower cost”

Professor Robin Shattock

Barriers to vaccination

There are many reasons why children and adults remain unvaccinated, but three key issues stand out – lack of access to basic amenities, storage and transport challenges and ‘vaccine hesitancy’.

Lack of access to basic amenities

The countries least likely to meet vaccination targets are countries in sub-Saharan Africa and Southeast Asia that have a lack of access to water, education and healthcare.

Vaccination targets are set by the Global Vaccine Action Plan, a 2012 document endorsed by 194 countries at the World Health Assembly. “We need to help manufacturers in low and middle income countries make vaccines more efficiently and at lower cost,” says Professor Robin Shattock, Head of Muscosal Infection and Immunity at Imperial College. “Most vaccines need to be made for less than a dollar a dose.” This is one aim of the Imperial-led Future Vaccine Manufacturing Hub (Vax-Hub), a £10m cross-disciplinary effort funded by the Department of Health and the Engineering and Physical Sciences Research Council.

Storage and transport challenges.

Vaccines that require cold storage (usually 2–8C, but can be much lower for some vaccines) can be difficult to transport and store appropriately because of the need for a ‘cold chain’. Freezing will damage some vaccines, such as cholera and tetanus. Some vaccines, such as MMR, can also be sensitive to light. The wrong environment can lower potency, or effectiveness.

Professor Shattock explains: “The last leg of the journey to remote places can be the most challenging. How can you keep a vaccine cold if you have to walk for a day in the Congo, or transport it through Syria? For example, the Merck vaccine against Ebola is saving lives but has to be stored at -80C.”

Colleagues are taking up the challenge. Jason Hallett is Professor of Sustainable Chemical Technology at Imperial and a core member of Vax-Hub. A formulation scientist, he has been developing salts that can stabilise vaccines in hot conditions. “Around 80 per cent of the cost of vaccination comes from storage,” he explains. But reaping the full benefits of such innovation requires policy and regulation to evolve accordingly. Professor Hallett says: “Once vaccines leave the manufacturer, nothing can be added except water. Any change to the formulation has to be done during manufacturing. The regulatory process for vaccines is restrictive and outdated.”

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THE FUTURE OF VACCINATION

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‘Vaccine hesitancy’

The phenomenon of delay or refusal has come to be associated with parents who believe vaccines are unnecessary or harmful. An unprecedented measles outbreak in New York this year, mostly among the Orthodox Jewish community, led to the declaration of a public health emergency, compulsory vaccination and $1,000 fines for non-compliance.

The UK Government is reportedly contemplating compulsory childhood vaccination. A similar policy was introduced in Italy this year, in response to the ‘anti-vax’ movement. A May 2019 paper in the journal BMC Medicine suggested a “No jab, no school” policy in the UK did not find favour in the public health and immunology community. Dr Arne Akbar, President of the British Society of Immunology, countered that other actions – improving access and coordination in health services, disseminating public information and training healthcare workers – should be tried “before resorting to this extreme measure.” Nonetheless Secretary of State for Health and Social Care, Matt Hancock MP has repeatedly **refused to rule out** compulsory vaccination. The WHO, among others, is currently using the hashtag #VaccinesWork to counter misinformation on Twitter and other social media platforms.

Diseases targeted by vaccines in development

The WHO **lists** more than 20 vaccines in development, targeting such diverse conditions such as Nipah virus, Chikungunya virus, norovirus, HIV-1 (the most widespread type) and staphylococcus aureus. These pipeline vaccines fall broadly into four categories.

Neglected diseases

Malaria and dengue fever are among many diseases that mainly affect low-to-middle income countries in Africa, Asia, Latin America and the Caribbean (a region sometimes described as the Global South), for which there has traditionally not been the market incentive to develop vaccines. The fragility of healthcare systems for delivering any vaccines also acts as a disincentive.

“There is a massive need to tackle neglected diseases and those associated with poverty,” Professor Shattock argues. “We clearly need sustained public investment on TB, malaria, dengue and HIV, where the timelines for [commercial] success are long and

the financial rewards uncertain." It would pay off in the long term, he insists: "The global community needs to change its thinking on costing vaccines: their added value to society is very much higher than their cost as final goods."

Zika is another example of a neglected disease associated with the Global South. It is a virus transmitted by the same species of mosquito, *aedes aegypti*, that transmits dengue fever,

Chikungunya and yellow fever. Zika was discovered in 1947 but rose to global prominence in 2015 after a large outbreak in Brazil. It was subsequently associated with birth defects such as microcephaly (an unusually small head).

Zika is on the WHO's Blueprint list of priority diseases, which are those that have epidemic potential but where no adequate countermeasures (vaccines, antivirals, other treatments) exist. One serious global concern is that climate change could expand the geographical reach of disease-carrying mosquitoes.

Zika is one of the diseases that inspired the launch of Vax-Hub. The hub aims to perfect a production process that can deliver tens of thousands of vaccine doses within weeks of a new pathogen being identified.

Dr Chris Chiu presents at The Forum workshop on Vaccines; he leads the Imperial Network for Vaccine Research.

HIV and non-communicable diseases

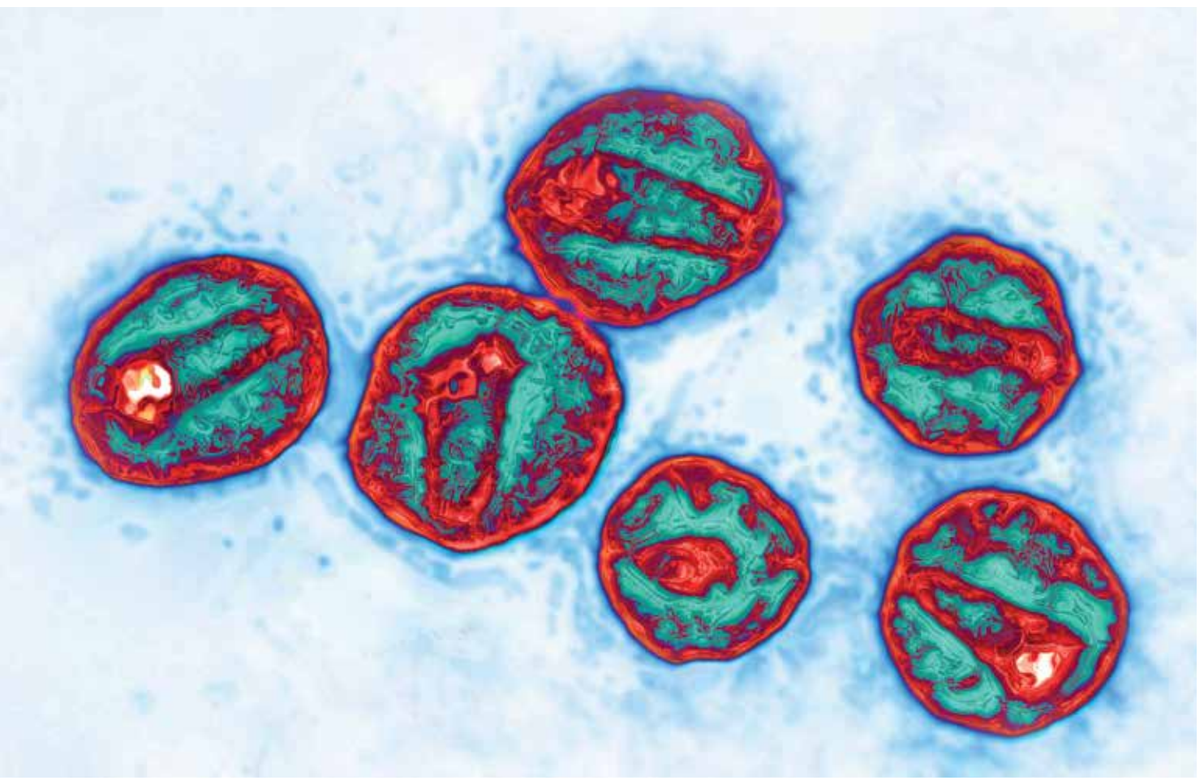
Vaccines are hugely versatile, and new research offers fresh ways of tackling some of the world's most notorious diseases, including foes such as HIV and cancer.

HIV

Professor Shattock is leading clinical trials of promising new HIV vaccines developed by the European Aids Vaccine Initiative 2020 (EAVI2020). The vaccines have been designed and produced in a record time. The team will test which combinations of proteins influence the development of protective antibodies.

He says: "Developing a fully protective vaccine against HIV is one of the biggest biological challenges of a generation. Some infected individuals can broadly neutralise the virus; studying their immune response has been a gamechanger.

"Our focus is getting a vaccine to people living in areas of highest risk of infection, where it can make the biggest impact, such as sub-Saharan Africa, but it also needs to be a global solution. Unfamiliar threats like Ebola get lots of attention but HIV still kills around 1.5m people a year."



Cancer

Vaccines can be either preventive or therapeutic. The HPV vaccine, against human papillomavirus, is a preventive cancer vaccine against a virus known to cause cervical cancer. It is offered routinely in more than 80 countries and has led to a **dramatic reduction in cancer cases**. The hepatitis B vaccine protects against a virus implicated in liver cancer.

Most cancers are not caused by viruses. Nonetheless, the immune system already has a capacity to recognise cancerous cells and clear them from the body. Therapeutic cancer vaccines, which treat cancers once they are found, could enhance this capacity. They are a form of immunotherapy.

DNA vaccines, for example, are designed to contain genetic material from the patient's tumour, explicitly flagging up to the immune system the genetic secrets of its adversary. None has yet been licensed for human use but it could be an exciting prospect in personalised medicine.

Diseases associated with antimicrobial resistance (AMR)

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Dr Elizabeth Klemm, project officer on vaccines for the Wellcome Trust, says that vaccines are "under-utilised" as a weapon against AMR. "They prevent infection, which cuts down on the carriage and spread of drug-resistant organisms. Our current work involves identifying which vaccines could have a big impact. A good TB vaccine, for example, would protect against drug-resistant strains."

A vaccine for typhoid has just been approved; it will help in Pakistan, Dr Klemm notes, where an outbreak of extensively drug-resistant typhoid has appeared for the first time.

She adds: "Also, widespread and inappropriate antibiotic use is a big driver of drug resistance. Vaccines for diseases that drive antibiotic use, such as the flu, should reduce the selective pressure placed on bacteria." In deciding whether to implement a vaccine, Dr Klemm urges countries to take its effect on AMR into account.

Diseases that have epidemic and pandemic potential

The 2014–2016 Ebola outbreak, which killed more than 11,000 people in Liberia, Sierra Leone and Guinea, highlighted how overlooked diseases can scale quickly into epidemics that cost lives, cross borders, ravage economies and threaten security. A pandemic is an epidemic that has escalated to have global reach, such as the 1918 outbreak of Spanish influenza, estimated to have killed 100m people.

Faster responses

"The 2014 Ebola outbreak was a wake-up call that the world needs to respond faster to outbreaks," says Professor Shattock. The timeline for developing new vaccines should be measured in weeks, not months and years.

That experience spurred the formation in 2017 of the **Coalition for Epidemic Preparedness** Innovation (CEPI), a partnership of public, private and philanthropic organisations. Founders include the governments of Japan, Norway and Germany, the Bill and Melinda Gates Foundation, and the Wellcome Trust.

CEPI is developing candidate vaccines against Lassa fever, Nipah virus and Middle East respiratory syndrome coronavirus (MERS-CoV). Future targets include Rift Valley fever, Chikungunya and 'Disease X' (the holding name for an as-yet-unknown pathogen that might emerge with pandemic potential). CEPI is also trying to develop 'platform technologies' to enhance the world's capacity to make vaccines at speed.

"We want to go from discovering a new pathogen to getting vaccine in a vial in 16 weeks"

Professor Robin Shattock

CEPI and Imperial have partnered on an RNA vaccine project. RNA vaccines are composed of the nucleic acid RNA, which encode antigen genes of an infectious agent. When administered to host cells, the RNA is translated into protein antigens that elicit protective immunity against the infectious agent

"We want to go from discovering a new pathogen to getting vaccine in a vial in 16 weeks," Professor Shattock explains. "Because we would be manufacturing synthetic RNA rather than growing the Ebola virus in containment facilities and deactivating it, everything can be done faster. The toxicology testing and the approvals would be quicker."

Prevention

Professor Wendy Barclay, who holds the Action Medical Research Chair in Virology at Imperial College, specialises in researching pandemic prevention, with a focus on avian influenza. The Barclay Laboratory at Imperial recently teamed up with the Roslin Institute near Edinburgh to see if gene-editing chickens – disabling a gene known to play a critical role in aiding the flu virus – can interrupt the chain of transmission.

"We were trying to understand the steps that an avian flu virus undergoes before it infects humans when we discovered this host gene that is crucial for the virus. If the gene-editing works as a concept, the big challenge will be developing policy about how to use the technology responsibly, public acceptance and regulation."

Vaccination, though, is a more immediate approach, and is paying dividends now: "China has been mass-vaccinating poultry and there have only been three human cases of H7N9 this season [last season saw 766 cases; H7N9 is thought to show pandemic potential]. If confirmed, it is an enormous achievement and highlights the power of vaccines to eradicate disease."

Professor Barclay also works on the seasonal flu vaccine – and thinks that policy changes could make a big difference: "The seasonal flu vaccine could be better than it is. Some years it is less than 20–30 per cent effective, in other years 60–70 per cent. We could achieve this higher rate more regularly by better matching a vaccine to circulating strains, growing it in the right substrate, using the acceptable adjuvants [ingredients that enhance a vaccine's effectiveness] and vaccinating at the right time.

"The problem here is that, for licensing reasons, manufacturers have to show a new product is superior and that requires huge, expensive studies. There is no incentive for these studies to happen if we continue to buy the less effective vaccine.

This year, Professor Barclay notes, elderly people will receive a trivalent vaccine [containing three flu strains]. Newer information suggests that a quadrivalent vaccine might be more effective but licensing restrictions prevent its use for the coming flu season. Professor Barclay asks: "What if the fourth strain turns out to be the most damaging? A more flexible process means patients can get the best vaccines as soon as we have them."

Building the infrastructure needed to fast-track the research and manufacture of new vaccines

> "The UK has a very strong academic base but an incredibly small number of vaccine manufacturers."
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The life sciences sector contributes £70bn annually to the UK economy and employs 240,000 people. The UK Government has indicated support for it through the Industrial Strategy, specifically through the Life Sciences Sector Deal.

As part of this, the country's first-ever Vaccine Manufacturing Innovation Centre is due to open at Harwell, Oxfordshire, in 2022. It is a three-way academic collaboration between Imperial, Oxford University and the London School of Hygiene and Tropical Medicine. It has received government funding of £66m, awarded by UK Research and Innovation (UKRI) through the Industrial Strategy Challenge Fund (in the Medicines Manufacturing portfolio). An extra $10m will come from commercial partners, including Janssen, Merck and GE Healthcare.

Professor Shattock explains: "The UK has a very strong academic base but an incredibly small number of vaccine manufacturers. The VMIC will help SMEs get going in this sector and stimulate investment in vaccine manufacturing."

Professor Adrian Hill, director of the Jenner Institute at Oxford University, echoes this: "During the Ebola outbreak, I kept being asked by politicians and journalists how long it would take to make enough Ebola vaccine for the UK. The answer was: we couldn't because there was nowhere to manufacture. The VMIC will serve two purposes: to make new vaccines quickly, and to support new industries and companies."

The world-class expertise at both Imperial and Oxford, Professor Hill says, underpins confidence, although Brexit remains a risk to funding: "The UK is internationally recognised in translational research. It is an amazing time to be in vaccine research."

Written for Imperial by Anjana Ahuja
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The Forum features

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