



PACIFIC LIFE RE

Vital Insights

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Pacific Life Re's
latest medical
research roundup

Climate change and its impact on mortality and morbidity

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Virus (RSV) Vaccine

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Welcome

Welcome to our first edition of Vital Insights. Here we've put together a collection of articles covering some of the major issues of the day with a specific focus on how they will impact mortality and morbidity. From the impact of climate change on our health, to a review of the effectiveness of new dementia drugs we hope this keeps you up to date with the latest in medical research.



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About Pacific Life Re

Our global team, comprised of the best minds in the industry, are not afraid to disrupt and challenge industry thinking to provide the best mortality, morbidity, longevity, and capital reinsurance products and services possible.

We pursue personalised, bespoke solutions for every one of our clients and our commitment to cutting-edge technology reflects our ambition to offer the most sophisticated answers to the most challenging reinsurance questions.

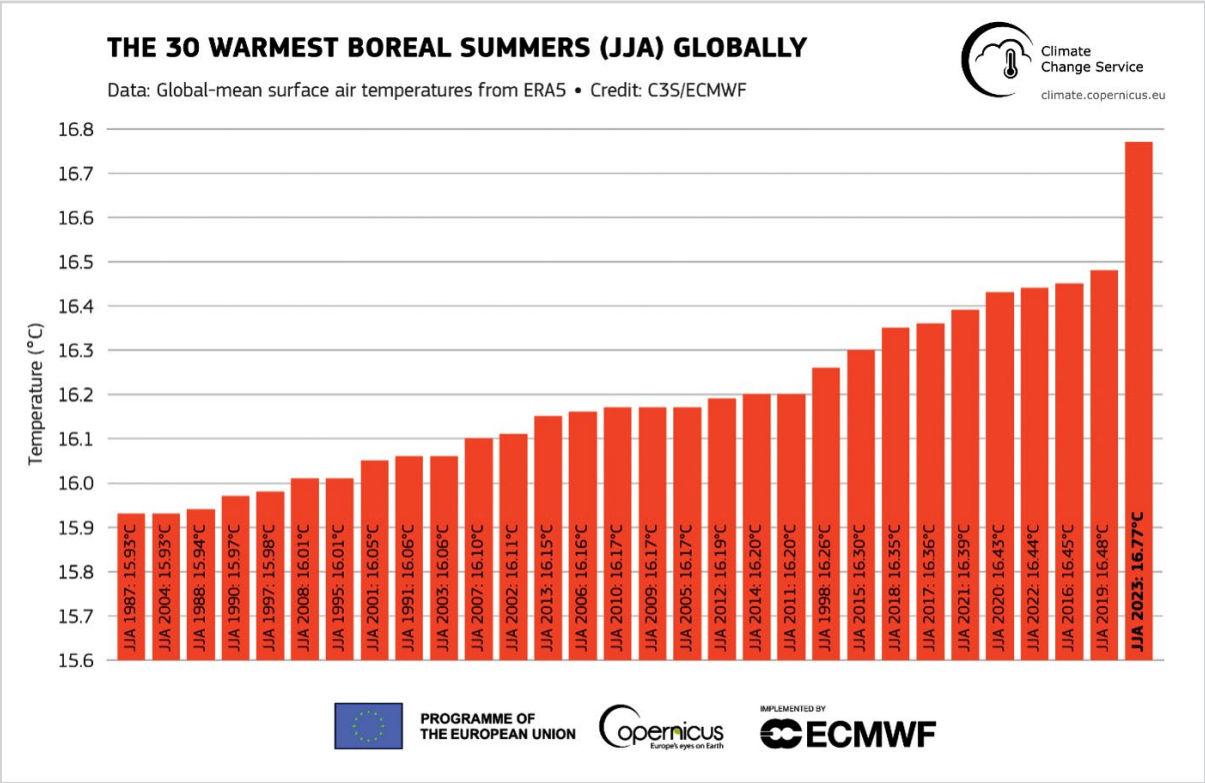
We are proud of our beginnings, and we celebrate our youth because it is what keeps us tenacious, agile and energised. We are equally proud of the security and freedom we possess from having the backing of our parent company Pacific Life. With a heritage of more than 150 years, Pacific Life provides strength and resilience to our business which enables us to bring our fresh and dynamic approach to the marketplace.

Climate change and its impact on mortality and morbidity

In 2023 we've seen soaring temperatures across the globe along with devastating storms and wildfires. Why is our climate changing and what impact is it having?

Is it just me, or is the weather crazy this year?

Summer 2023 in the northern hemisphere was the hottest in human history¹. In fact, as illustrated below, this was by some distance. The June-August season was 0.66°C (1.19°F) above average summers and around 0.30°C (0.54°F) hotter than any prior season.



However, talk of fractions of a degree are quite easy to write off as inconsequential. Risks to life, health and property derive not from slight increases in average temperature, but from extreme events downstream of these. While extreme events have always occurred, the number and intensity of these have without doubt increased. 2023 has seen more than its fair share of climate-related disasters.

In North America, periods of hot and dry weather led to significant wildfires, including the destruction in August of the Hawaiian town of Lahaina in the state’s worst natural disaster, and the deadliest fire in modern US history². In California, scientists believe climate change was a significant factor contributing to the huge increase in land area affected by wildfires during summer months . Many other parts of the United States and (especially) Canada were also affected by fires this summer. In Canada, the area burned was over 170,000km³, which is around half the size of Germany.

Record-breaking heatwaves in Southern Europe and Turkey saw temperatures over 45°C for extended periods, including

in Greece and Italy where extensive fires, especially on Sicily, caused significant damage⁴. In South America, despite July being mid-winter, some parts of Argentina and Chile set extraordinary all-time temperature records, more than 20°C above normal for the time of year.⁵

Severe droughts also occurred in many parts of the world, including several parts of Europe⁶, with the resulting negative impact on crop yields and water supply.

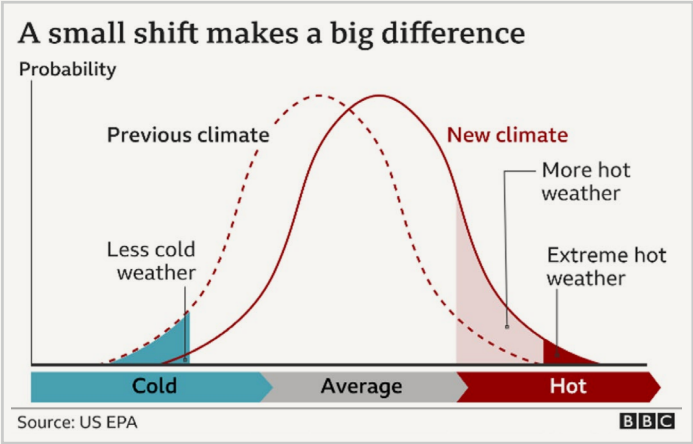
To make things worse, on top of sweltering temperatures, several regions including Beijing in China⁷, Fukuoka and Oita in Japan⁸ and parts of South Korea⁹ also experienced torrential rainfall, with flooding and landslides. Australia has also seen flooding in recent seasons, including in New South Wales in late 2022 which became the nation’s most expensive natural disaster.¹⁰ More recently, thousands died in flooding in Libya in September. There were heatwaves in southern Italy as well as extreme hailstorms in the north of the country which produced the largest hailstone ever found in Europe. As can be seen below, it was 19cm long.



What is causing all of this?

These events are not coincidental. Recently, global sea surface temperatures have escalated at an unparalleled pace to hit record highs¹¹. This is thought to be due to a combination of drivers, including long-term human-induced global warming and the so-called El Niño phenomenon. El Niño is a recurring event which is part of cyclical variations in winds and sea temperatures. It affects ocean currents causing the release of extra heat from warmer waters into the atmosphere to drive air temperatures up, with wide ranging consequences, including more extreme weather conditions. A slight rise in average temperatures has a significant impact because it causes the entire range of daily temperatures to shift towards warmer levels, increasing the likelihood and intensity of days with more extreme heat.

This is shown below, but note that it may be more likely the distribution of typical daily temperatures widens, rather than uniformly shifting toward the right (i.e. towards hot days). One consequence of this would be that we might see more hot days without necessarily seeing so many fewer cold days as we might expect, with implications for mortality assessed below.

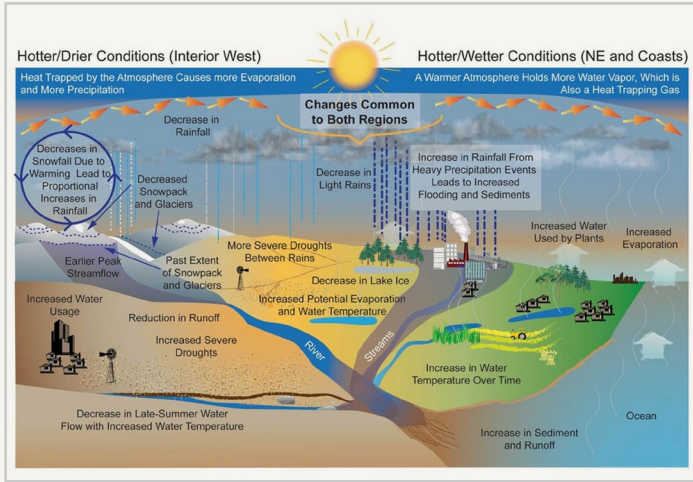


Water vapour has played a vital role in sustaining a habitable temperature on earth for eons. In fact, without it, the planet’s surface temperature would plummet to around 33°C (59°F) colder than it is now! Warm air holds about 7% more water vapour, per 1°C increase in temperature¹². Hence warmer air richer in water vapour prevents more heat from escaping, absorbing it instead creating a so-called ‘positive feedback loop’.¹³

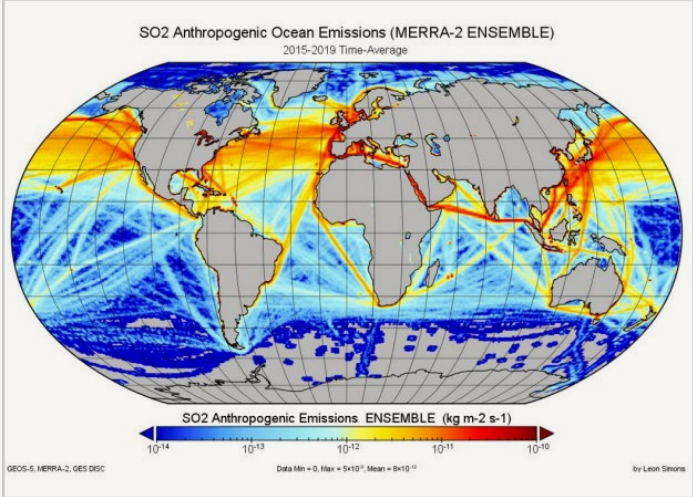
However, at higher temperatures, increased concentrations of water vapour in the air exacerbate the greenhouse effect. In fact, water vapour is the most abundant greenhouse gas on earth, responsible for approximately 50% of the greenhouse effect, through which the sun’s heat is trapped in earth’s atmosphere. It is likely this process was further exacerbated by a large sub-sea volcanic eruption in Tonga in 2021 which released an unusual quantity of water vapour into the atmosphere.

Water vapour is also a critical component of the planet’s water cycle, facilitating the movement of water in various forms throughout the atmosphere, land, and oceans. Warmer

temperatures speed up the water cycle which aggravates weather conditions. Wet regions become wetter and dry regions become drier, the mechanisms for which are shown in the graphic below.¹⁴ As air contains more water vapour, it also holds more latent heat that fuels intense windstorms and thunderstorms. The acceleration of evaporation of water from land also results in soil drying out. Instead of infiltrating the soil, subsequent intense rainfall on parched ground increases the rate of water runoff into rivers and streams, increasing flood risk.



There is one additional factor which may contribute to the sudden increase in sea and air temperatures, which can best be described as ironic. Global shipping is a material contributor to air pollution. Measures to reduce sulphur emissions from ships include strict new measures mandating use of low-sulphur fuels. However, it turns out sulphur emissions in the atmosphere were helping to reflect some heat away from the planet. Since the change has been successful, there is now a lot less sulphur in the air, with the undesirable side-effect that more heat from the sun now reaches the surface of the planet. In effect, this pollution was masking some of the effects of climate change, especially in the busy shipping lanes shown on the following page. The sudden change is the equivalent to around two additional years of emissions and its effect is concentrated on the North Atlantic and North Pacific Oceans.¹⁵



What does this mean for Life and Health insurers?

Mortality and morbidity impacts

Despite the increased number of climate-related natural disasters, their impact on overall mortality is currently minimal, especially in high-income countries. Therefore, even the noted increase in such events may have a muted impact on future mortality. Naturally the impacts will vary by territory depending on factors including local climate, health infrastructure and underlying health of the population.

Despite growing prominence of wildfires, and the recent sad death toll in Hawaii of 97, the direct impact of fires on population mortality rates is typically modest. The resulting pollutants can also have secondary impacts on morbidity, for example by worsening respiratory conditions. However, these are harder to calculate. One study estimated that across a large area of central California with a total population in excess of 10 million, exposure to unhealthy particles known as PM2.5 during the California wildfires of October 2017 resulted in an additional 308 respiratory, cardiovascular, and asthma-related hospital admissions.¹⁶

Heatwaves

Heatwaves are probably the most consequential events for human health as they can affect large, populated areas for extended periods. Still, we should recall that in temperate climates there are typically more deaths associated with cold weather than hot weather, and that if periods of intense cold reduce as part of climate change there may be substantial offsets to any increase in summer deaths. Hence, on balance, they are unlikely to be a strong driver of additional impacts on population health or, consequently, on life and health insurance books in such markets over the medium term. However, some reasonable future predictions suggest this impact may not initially happen as neatly as this logic suggests. Instead of all temperatures shifting uniformly upwards as the climate warms, the range of

daily temperatures may widen. This would mean more hot days, but initially little reduction in cold ones, reducing any mortality offset we might otherwise expect due to a reduction in the number and intensity of periods of cold. The annual pattern of deaths, currently materially more concentrated in winter months, may slowly change. The medium-term prospects are less clear, with uncertainty around the trajectory of average temperatures as well as our collective ability to make necessary changes to global infrastructure including in relation to power generation, transportation, agriculture and water management.

Heatwaves damage health by causing illnesses like heatstroke. In hot weather, blood vessels dilate so that more blood can flow towards our skin and cool us down. However, dilating blood vessels force our heart to work harder. This means that those at highest risk in hot weather are those with existing cardiovascular problems. We might also see respiratory conditions increase in number and severity. Poorer air quality is likely to accompany climate change and higher concentrations of pollutants can exacerbate conditions like asthma and chronic obstructive pulmonary disease (COPD).

Infectious diseases

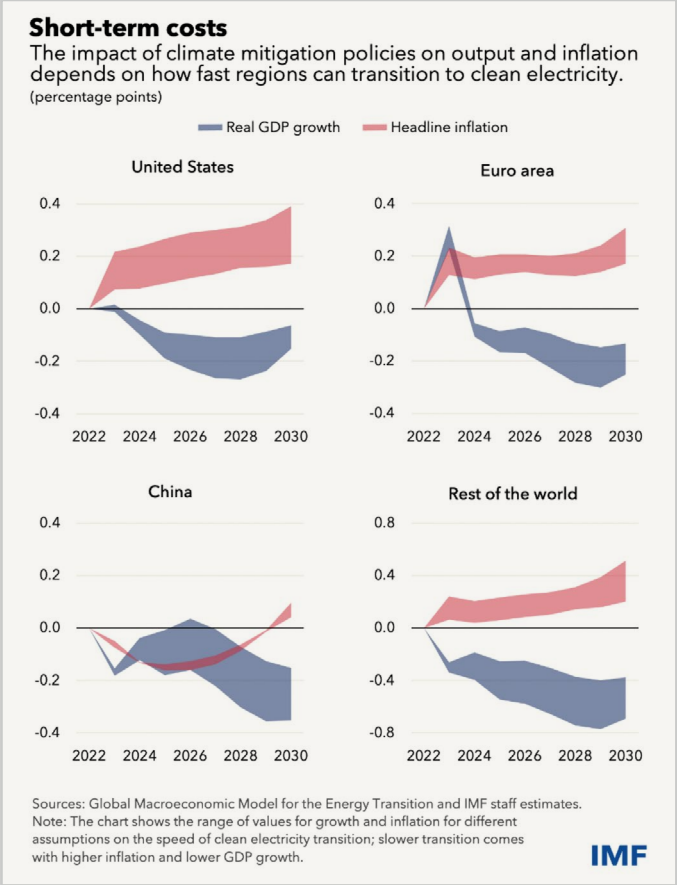
Incremental changes in the dynamics affecting circulation of infectious diseases are also likely. This includes vector-borne diseases such as dengue and malaria. For example, a recent paper (not yet peer-reviewed) found that climate change has driven expansion of dengue fever risk in Vietnam.¹⁷ Some cases of locally-acquired dengue fever were also identified in Italy and France this year. This is highly atypical.¹⁸ While these diseases are mainly influenced by increasingly warm temperatures, others also relate to weather becoming increasingly wet, including West Nile virus.

All of the above impacts are likely to be slow and, in higher-income locations, relatively small overall. In all cases, vulnerable groups, such as children and the elderly, are expected to be more adversely affected due to their heightened susceptibility to the health impacts of climate change.

Economic impacts

Long-term sustainability is increasingly recognised as an important feature of investment assets. Some of this is altruistic, but there are also significant risks associated with entities materially exposed to less sustainable practices such as heavy usage of carbon. These entities may face higher costs of doing business and associated significant shifts in asset values.

Achieving progress towards sustainability will undoubtedly entail short- to medium-term economic costs concentrated in, but by no means limited to, the companies most exposed to these transition risks. The chart on the following page shows the IMF’s anticipated range of impacts on entire economies of the transition to clean energy on GDP (blue) and inflation (red).



In addition to encouraging the above changes, the impacts of climate change can also exacerbate economic pressures. For example, increased costs of food due to climate related periods of scarcity would encourage inflationary pressures. The indirect impacts of periods of recession or austerity on health and healthcare may yet prove to be more material in terms of mortality and morbidity outcomes in the long term than the physical risks discussed above.

Conclusion

Climate change already affects many aspects of our lives. Seemingly small rises in temperature can, and already do, cause a proliferation of headline-grabbing natural disasters on every continent, with direct implications for human health. As devastating as these events are, some of the largest impacts for life and health insurers likely lie elsewhere. The gradual increase in number and intensity of heatwaves; changing patterns of pollution, and of infectious diseases; and longer-term knock-on impacts from economic disruption all represent more insidious, but potentially materially more impactful, ways in which the issue can impact the health of insurers, and the lives they insure.



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Deep dive: Alzheimer's

Total deaths from dementias in high-income countries have almost quadrupled in the last 20 years, yet so far medical science has very few answers. This article looks at the recent emergence of the first drugs which may be able to modify the effects of this terrifying disease.

Alzheimer's disease is one of the most common causes of death in the world. Usually a disease of older age, data suggests dementias, more broadly, are now the second or third leading cause of death in high-income countries, depending on whether cancers are all counted together or not. According to the WHO, Alzheimer's recently overtook strokes and is behind only ischaemic heart disease.

Total deaths from dementias in high-income countries have almost quadrupled in the last 20 years, yet so far medical science has very few answers. This is not for want of effort. Scientists have dedicated vast amounts of time and money seeking ways to at least slow down, if not reverse or prevent, this degenerative disease.

This article looks at the recent emergence of the first drugs which may be able to modify the effects of this terrifying disease.

Hope at last

For decades, scientists have struggled to understand what causes Alzheimer's and develop drugs which can arrest, or at least slow, its progress. The biological mechanisms causing this disease remain poorly understood, and there are probably several which contribute. However, of these, one dominates much recent Alzheimer's research.

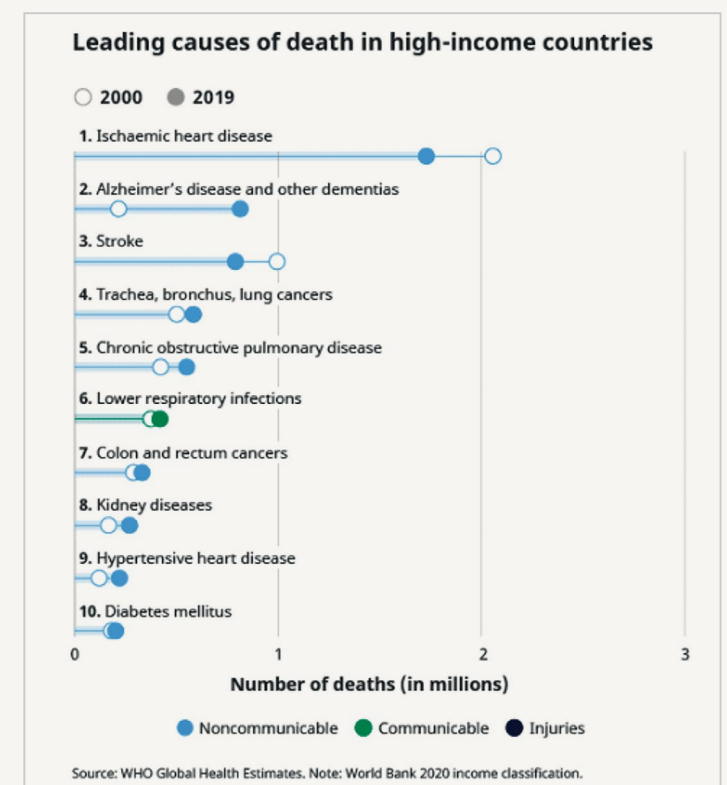
Many scientists believe that the disease is caused by aggregations of proteins in the brain. This theory, known as the 'amyloid hypothesis' states that strands of a protein, known as amyloid beta, clump together to form deposits known as amyloids. Over time, more proteins become stuck to these deposits, eventually forming plaques which are large enough to disrupt communication between cells in the brain. Immune cells are activated, causing inflammation and, ultimately, the destruction of brain cells.

If this is how Alzheimer's develops, then it makes sense to try to slow its progress by tackling these amyloid deposits. Three new drugs have created headlines recently as potential 'game-changers' for people with Alzheimer's, and this is exactly how each of them tackles the problem.

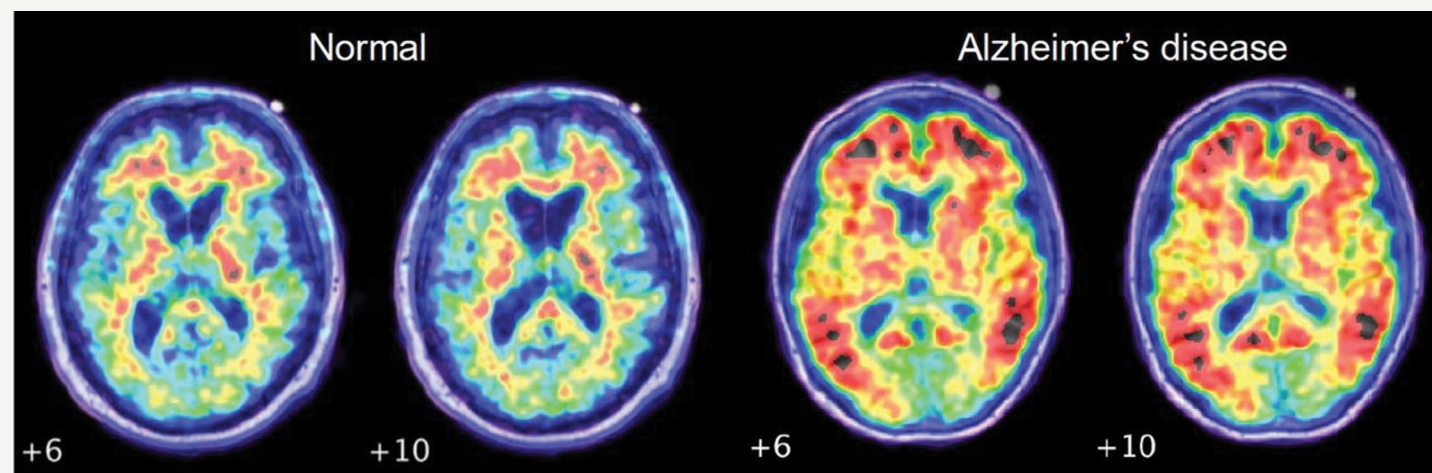
The first, aducanemab, was conditionally approved for use in the United States in 2021.¹ The drug was demonstrably able to reduce amyloid plaques in people using it, but failed to meet its primary endpoint of clinically improving patients' symptoms such as memory loss. As such, its approval was controversial. Lacking evidence that it would make any noticeable difference to patients, understandably, many doctors refused to prescribe it. Medicare – federal health insurance for Americans aged over 65 – and regulators elsewhere, including the UK and EU, also did not approve the drug for use.

Next on the scene was lecanemab. This too showed it could reduce amyloid plaques in the brain - dramatically so, in fact. This time there was also more positive news for patient outcomes, with trials suggesting it slowed decline in memory and thinking by a modest 27% after 18 months of treatment. Given the low bar for approval set by aducanumab, it is perhaps unsurprising that lecanemab was fully approved in July 2023 in the USA.² Regulators elsewhere continue to assess the trial findings to determine if wider approval will follow.

Very recently, donanemab became the third drug to show some success in this area. It again demonstrated good success at reducing the underlying plaques, with substantial reductions in measurable plaques seen in around 80% of trial participants.



Although its abilities to improve clinical outcomes, e.g. memory loss, for patients were again modest, it appears at least as impressive as lecanemab. Disease progression slowed by around one-third in one sub-group of patients who had lower levels of another protein called tau. This effect reduces significantly to 22% slowing if people with higher levels of tau are included. The drug's approval in the US is pending but expected to be granted.



Tempering expectations

It is undoubtedly exciting that medical science is reaching a point where it can make inroads against this disease. However, we must note the limitations of these drugs. The most fundamental of these is that their impacts on the symptoms of Alzheimer's remain unspectacular, and limited to those with early-stage disease. Focusing on donanemab, because it appears the most promising, its trials actually produced counter-intuitive outcomes.

On the one hand, the drug achieved statistically significant improvements in patient outcomes, meaning that it is highly likely that the group taking the drug fared better than the one taking a placebo, and that the drug was the cause of this difference.

However, clinical significance - such as cognitive changes in a patient that can be measured - is in doubt. Progression of Alzheimer's is difficult to measure and more subjective than for many diseases. The disease is measured by administering tests seeking to determine patients' abilities in areas such as word recall, orientation, memory and word-finding, among many others. On one test used in the trial, changes of at least 5 points on the scale are the minimum considered clinically significant³, and yet donanemab's trial only led to an improvement of around 3 points⁴. This means an average person using the drug, or their family, would likely not notice any difference after using the drug for 18 months, despite its claimed successes. Longer-term impacts have not been tested, and the claimed significant improvement only emerges when we consider the trial participants at a group level.

The drugs also present practical problems. For one, they are not without side effects. Rare but serious side-effects include brain swelling and small strokes, with serious side effects affecting 1.6% of participants in donanemab's trial, and a much larger 24% developing other less severe reactions to the drug. These drugs are also administered via infusion as an intravenous drip. Patients need to attend a clinic for up to an hour each week to receive the medication, although one new candidate drug - remternetug - is seeking to determine if an injectable alternative is viable, a bit like an EpiPen for diabetics.

Finally, there is a bittersweet result implied by many of the trial results discussed above. These drugs set out to tackle amyloid deposits in the hope that doing so would significantly alter the course of Alzheimer's disease. They are actually very effective at the physical reduction of amyloids, meaning the muted impacts on patient outcomes are a concern. In other words, we may not have much scope to tweak the drugs to make them better, because they already meet their primary (physical) objectives. Instead, there are likely other entirely separate causes of the disease which we are not yet targeting at all.

These drugs are an important start. They are a proof of concept that Alzheimer's disease can be modified, and provide some hope for further developments in future. However, those hoping we are on the cusp of turning Alzheimer's into a manageable disease may be disappointed for a while yet. We will likely need to see significant further progress, including in areas with no successful drugs yet, before we can realistically hope to materially reduce the burden caused by this fearsome disease.



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New Respiratory Syncytial Virus (RSV) Vaccine

COVID-19 has stolen the limelight from other respiratory viruses in recent years. However there are plenty of other common viruses which can have serious health consequences, among them Respiratory Syncytial Virus, or RSV.

RSV is extremely common, infecting an estimated 64 million people globally each year, and killing around 160,000 of them¹. By comparison, influenza kills between 290,000 and 650,000 per year². Primarily affecting the lungs and upper respiratory passages, RSV is typically mild when experienced by healthy adults. However, its impact can be more severe for children under five and the elderly. It's therefore extremely encouraging that vaccines and treatments are emerging which can be used in each of these age groups.

In the US, the Food and Drug Administration (FDA) has awarded approval to the first RSV vaccine for over-60s, which is already available in American pharmacies, with wider approvals expected in the coming months. This vaccine, Arexvy, has been produced by GSK, but another candidate from Pfizer (Abrysvo) also recently secured approval. What's more, a third candidate from Moderna recently has shown promise in late stage trials. The RSV vaccine market presents pharmaceutical companies with an estimated annual \$10bn opportunity, so perhaps it is no surprise there is such a healthy pipeline.

For infants, the most successful treatment candidates so far have been antibodies, not vaccines. Most notably an antibody known as nirsevimab, given preventively as a single-dose, recently received

authorisation in both the US and UK. Trials showed this drug reduced the risk of severe infection by around 70% compared to placebo. One vaccination intended for expectant mothers is also awaiting approval.

RSV is endemic and never likely to be eliminated. However, together, these products are expected to materially improve outcomes for those affected.



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An end in sight for AIDS?

A new UN report reveals optimism about a possible end to the global AIDS epidemic.



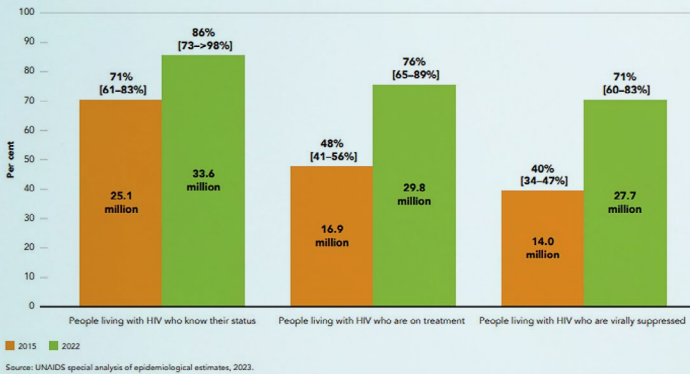
The UN has set so-called 95-95-95 targets. This means:

- 95% of people living with HIV know their status
- 95% of those who know they have HIV are on antiretroviral treatment
- 95% of people on treatment are successfully virally suppressed

Many countries already meet these targets. This increasingly includes countries in the worst-affected parts of the world such as sub-Saharan Africa where five nations already meet these standards. Around the world another 16 are close to doing so, half of them in Africa.

Knowledge of HIV status, treatment and viral load suppression levels have risen substantially

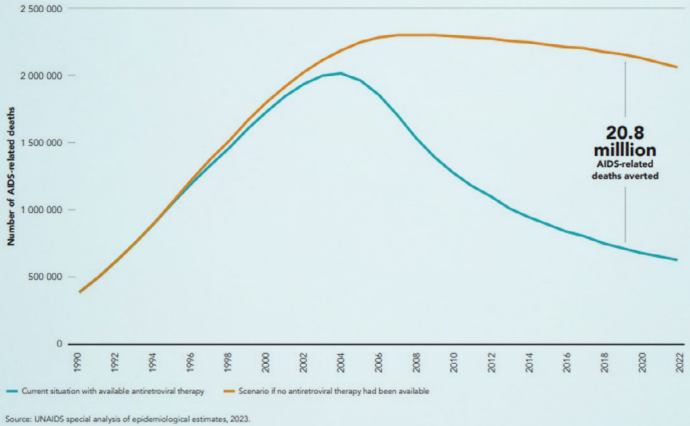
Figure 1.2 Percent and number of people living with HIV who know their HIV positive status, are receiving antiretroviral treatment and are virally suppressed, global, 2015 and 2022



Access to treatments continues to expand rapidly. At present 30 million out of 39 million estimated to be HIV positive globally (77%) are on treatments and an additional 1.6 million received treatment in each of 2020, 2021 and 2022. Treatment has averted around 20 million deaths since the turn of the century (see graph).

HIV treatment averted almost 21 million AIDS-related deaths between 1996 and 2022

Figure 0.1 Number of AIDS-related deaths: current situation versus scenario without available antiretroviral therapy, 1990-2022



Notably the estimate for total numbers affected comes with wide uncertainty (95% confidence that it is between 33 and 46 million) reflecting poor infrastructure in many badly affected countries.

AIDS is the name given to the collection of immune related diseases associated with the damage caused by HIV. Claims in this report that it could be eliminated by 2030 do seem optimistic considering the disease claimed a life every minute in 2022. However, two decades ago deaths were four times as high and the current trend is promising. This creates cause for optimism that further substantial improvements can be expected in this decade.¹

Numbers of new HIV infections, especially among children and young women, have halved since 2010, meaning the numbers of new people at risk of AIDS is rising far less rapidly.

The principal challenges to progress relate to gender inequalities, violence, stigma, discrimination, and harmful laws, including against homosexuality. Improvements in Africa are not mirrored in Asia and the Pacific where new HIV infections are rising. Countries achieving success tend to be more successful at addressing the above challenges, though significant shortfalls remain. Globally, investment is falling slightly, with funding gaps in Eastern Europe, Central Asia, the Middle East and North Africa.

HIV/AIDS has now been around for long enough that its continuing impacts on mortality can feel like an inevitability. However, these impacts have diminished greatly in recent decades, and there is real hope that a combination of government-led policy and community-led programmes could build on that progress to further reduce the footprint of the disease in the coming years.



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Anti-vaccine sentiment increases risk of measles outbreaks

Vaccine technologies have continued to improve greatly in recent years. However, vaccines are little use if people refuse to use them. Here we look at the precarious position of measles, a well-known but little-understood serious condition, which is held in check in most countries only because of high vaccine uptake.

Measles remains one of the most contagious diseases known to science. Its potentially disastrous consequences, including meningitis, blindness and pneumonia, have generally been forgotten since high rates of vaccination have greatly reduced cases in many wealthier nations. However, the COVID-19 pandemic has accelerated trends in people who are sceptical of the efficacy and value of vaccines, including the MMR vaccine, which protects children against measles, mumps and rubella.

A recent poll found that 23% of Americans feel it is probably or definitely true that the MMR vaccine has been proven to cause autism, even though this finding has been widely discredited. 20% of those surveyed said they believed more people had been killed by COVID-19 vaccines than by COVID-19 itself.¹

Rates of vaccination required to achieve herd immunity for measles are exceptionally high, likely around 95% due to the highly contagious nature of the disease. A report from the UK government highlights the increasing risk of a resurgence of the disease associated with low vaccine uptake. The risk is greater in areas with lower uptake. In the UK context, uptake in London is unusually low: only 74% of children have received the recommended two doses of MMR by age 5.²

In 2021 there were only 2 cases of measles in the UK. This rose to 54 in 2022. However, don't be fooled by the small numbers. If the reproduction number rises above 1, then a tipping point could be reached. If an average case passes the disease to more than 1 other person, leading to exponential increases in the disease, a far larger outbreak could occur. The report concludes that London could see an outbreak of between 40,000 and 160,000 cases. Essentially continuing until the susceptible population has been exhausted by new infections. Estimated fatality rates range from 1 in 500 to 1 in 3000³, although the report suggests 20-40% hospitalisation rates are expected. People who have been vaccinated usually have lifelong immunity.

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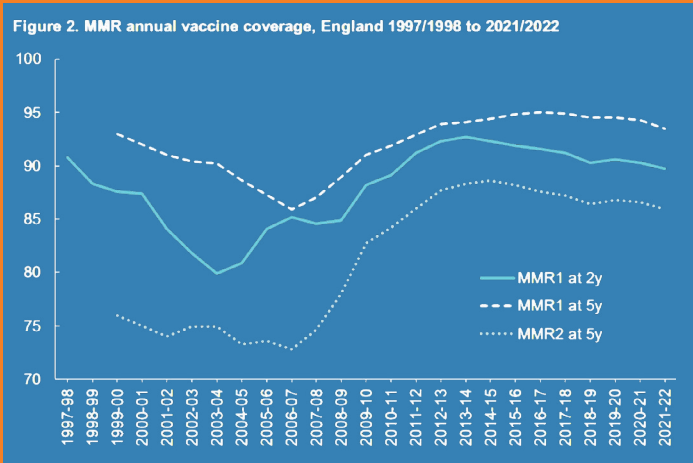
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The recommendations include catching up on missed vaccinations for children and young adults.

US vaccination rates overall are at 93%, a little higher than the UK, though in 9 states, plus the District of Columbia, rates are below 90%.⁴

The quick, safe, successful development of effective COVID-19 vaccinations was a triumph of science. However, some of the public health messaging surrounding their rollouts, and the wider pandemic response, may have had unintended effects including growing suspicion of recommendations emanating from national and multi-national organisations. Measles vaccination rates vary substantially, from 99% in some countries to below 50% in others.⁵

Even in countries with relatively high rates, we should remember those who reject vaccines are not distributed evenly throughout the population. Within any population, some groups will be at higher risk due to lower vaccine uptake. Any group of people likely to come into contact with one another, where material numbers are unprotected, is at risk of an outbreak – something that could be easily prevented using widely available vaccines.



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Does a common sweetener cause cancer?

The International Agency for Research on Cancer (IARC), the cancer research arm of the WHO, recently classified the common sweetener aspartame as a possible cause of cancer in humans.

The International Agency for Research on Cancer (IARC), the cancer research arm of the WHO, recently classified the common sweetener aspartame as a possible cause of cancer in humans. This work was in conjunction with the Joint Expert Committee on Food Additives. This means it could cause cancer. Aspartame is used in many food products from breakfast cereals and diet soft drinks, to some ice creams and gelatin.

However, despite the worrying headline, the threat is very small. Safety is not a major concern at doses commonly ingested. The classification assigned to aspartame is 2B, defined as 'possibly carcinogenic to humans'. To give some idea of the company it keeps in this category, 2B also includes aloe vera, 'carpentry and joinery', and the use of talcum powder on the perineum, alongside a long list of chemicals.¹

The classification is assigned, somewhat counterintuitively, based on levels of certainty that a risk exists, not on the actual level of that risk. There have been no changes to the recommended daily intake of aspartame, which equates to between 9 and 14 cans of soft drink per day for the average adult (approximately half of a standard bucket!), and even this level has a large built-in safety factor.

Overall, this development should not be a cause for concern.

And we shouldn't all rush to the conclusion that sugar-sweeteners are safer than artificial ones, either. Interestingly, a separate recent study found that women who regularly drank soft drinks sweetened with sugar in the 1990s were at increased risk of liver cancer and other chronic liver diseases 20 years later.² This relationship only existed when comparing people who drank these drinks daily against those who very rarely consumed them, and in any event the study is not powered to say whether the sugar was the cause of the later disease.

These are both interesting studies, and it is important to study links between common food additives and health. However, it is important not to exaggerate the results. Neither of these studies should cause much concern for people who take either artificial- or sugar-sweeteners in moderation.

References

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