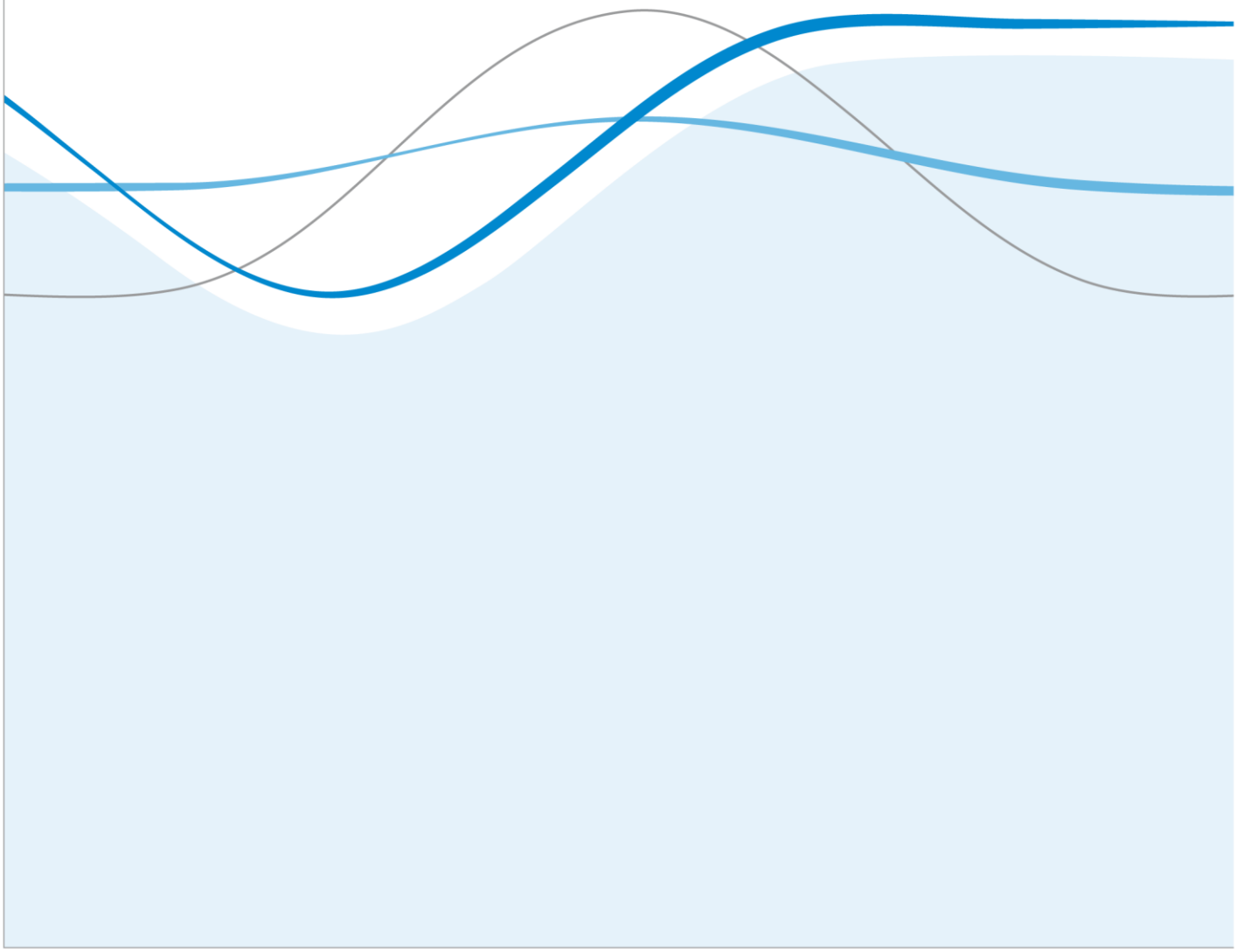
Office of Health Economics Consulting

Consulting Report

The Impact of New Medicines in the NHS: 70 Years of Innovation

August 2018

Chris Sampson, Phill O'Neill, Paula Lorgelly



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EXECUTIVE SUMMARY

The NHS in England and Wales came into existence on the 5th July 1948. It provided coverage for a range of approved medical and pharmaceutical interventions. This resulted in rapid growth in the use of medicines and improved public health with its associated improvements in economic growth and development.

This report demonstrates the contribution and impact of medicines to the health economy in the UK throughout the 70-year history of the NHS. Through interviews with experts we identified a shortlist of the most important medicines to have been brought to market, and from a review of the literature and evidence base we attempt to quantify the benefits of these key medicines in terms of health and economic outcomes. We additionally consider the broader impact of medicines and drug development to the health care environment.

Our interviews with experts identified a shortlist of ten important new medicines introduced in the NHS in the last 70 years. These were selected from a longer list of 37 on the basis of the frequency that they were cited by interviewees and the strength of feeling about the magnitude of their positive impact in the NHS.

The ten medicines are:

- Chlorpromazine
- Polio vaccine
- Oral contraceptives
- Second to fourth generation penicillins
- Beta blockers
- Beta2 agonists
- Tamoxifen
- Immunosuppressants
- HIV/AIDS antiretrovirals
- MMR vaccine

Our evidence search identified a variety of benefits encompassing improvement in clinical outcomes, survival benefits, quality of life improvement, greater health service efficiency, and wider societal impacts. It is important to note that the level of quantification of these benefits is variable, meaning that it is difficult to definitively aggregate the value of these benefits.

Our analysis of the interviews identified seven themes, each representing a factor that has played an important role in determining the impact of new medicines: i) the value of innovation, ii) complementarity and spillovers, iii) substitution, iv) policy, v) evidence, vi) understanding, and vii) collaboration. These themes highlight a variety of ways in which policymakers can facilitate positive impact from new medicines. Their role should be considered in the use of medicines in the NHS over the next 70 years and for new medicines currently in the development pipeline.

1. BACKGROUND

2018 marks the 70th anniversary of the National Health Service (NHS) and the Association of the British Pharmaceutical Industry (ABPI), and 60 years since the first ABPI Code of Practice. Countless advances have been made in health care over the last 70 years, with many innovations in pharmaceuticals improving patients' outcomes.

Following the Beveridge Report of 1942, and the passing of the National Health Service Act in 1946, work began to establish the NHS in England and Wales on the 5th July 1948. Existing coverage was extended to include medical and pharmaceutical benefits for the entire population. This resulted in rapid growth in the use of medicines (Cutler, 2003). The first ABPI Code of Practice was published in 1958 to ensure that the promotion of new medicines used in the NHS was conducive to patient benefit.

There are a variety of means by which the development of new medicines – available on the NHS – improve patient health and contribute to the economy. New medicines may address health problems for which no treatment was previously available. New medicines can also complement existing treatments, making them safer or more effective. Alternatively, innovations may result in the replacement of older medicines. The NHS can also benefit from the development of new medicines by improving value for money. In order to support an environment in which medicines development can contribute efficiently to improved patient outcomes in the NHS, it is important to understand these mechanisms of impact and to identify which medicines have brought the greatest benefits during the history of the NHS.

In 1980, The Office of Health Economics (OHE) published a report titled 'Medicines: 50 Years of Progress 1930-1980', which commemorated pharmacological progress over the period (Wells, 1980). The report discussed research and development and identified the impacts of key medicines including penicillin, streptomycin, anaesthesia, steroids, chemotherapy, and psychotropic medicines. A wealth of epidemiological data has become available in the intervening years, and important new medicines have been developed and approved for use in the NHS.

1.1. Objectives

With this study, we seek to demonstrate the contribution of medicines to the health economy in the UK, throughout the history of the NHS.

Our research questions are:

- What are the most important medicines to have been brought to market in the last 70 years?
- What has been the benefit to the NHS of key medicines in terms of health and economic outcomes in the last 70 years?
- What additional impacts do these medicines have on the health care environment?

The 'most important medicines' represents a shortlist of those medicines perceived by experts to be the most important in the history of the NHS in terms of their contribution to health and economic outcomes. We adopted a broad definition of health and economic outcomes, including mortality, quality of life, productivity, and health service efficiency, as applicable.

2. METHODS

Our study collates qualitative and quantitative data to answer our research questions, using interviews and literature review. The shortlist of important medicines was identified using qualitative methods in order to avoid it consisting solely of those (more recently developed) medicines for which quantitative data are more readily available.

2.1. Interviews

To ground our approach, we first undertook to identify and review existing historical accounts of medicines development in the UK since the introduction of the NHS. This included a review of the literature, and exchanges with academics, research groups, and organisations with an interest in the history of medicines development, such as the British Society for the History of Pharmacy and the British Society for the History of Medicine.

Using the information gathered, we designed a semi-structured interview guide (see Appendix) covering i) general perceptions of the impacts of medicines, ii) medicines development through time, and iii) new medicines in a range of contexts. The interview guide consisted of open ended questions and focused on the interviewee's views about what were the most important medicines – in terms of health and economic impact in the UK – introduced during the history of the NHS. These medicines (or classes of medicines) were not presupposed, no prompts were given, and medicines were only specified by interviewees. For medicines identified as being important by the interviewee, the interviews then went on to explore the nature of these medicines' impact.

Experienced pharmacologists, pharmacists, and clinicians were invited to attend an interview between January and March 2018. Interviewees were offered an honorarium and interviews were conducted either face-to-face or by telephone. Candidates were selected in order to provide expertise from a range of clinical fields and settings. Interviewees were chosen on the basis of their anticipated ability to provide information about the role of medicines in the NHS in terms of the extent to which they have improved health and economic outcomes over the last 70 years. Recruitment to the study was guided by saturation, whereby interviewees were invited until no new important medicines or themes were identified. We anticipated that around 10 interviews would be sufficient to reach data saturation with respect to the most important medicines.

Interviews were recorded and transcribed to facilitate a thematic analysis of the qualitative data. After familiarisation with the data, an initial set of codes was generated in line with the research questions. Namely, the coding process identified passages in the text where the interviewees specified either i) a medicine as being important, or ii) a contextual factor that could influence the impact of medicines. Coding was completed using the Coding Analysis Toolkit (Lu & Shulman, 2008).

Subsequent to the coding process, semantic themes were identified within the two groups of codes. These themes were used to prepare a long-list of candidate medicines to be taken forward in the study and to identify key themes in relation to the impact of medicines in the NHS. Interviews were also used to identify supporting sources and data.

Based on the frequency of citation of individual medicines, and interviewees' strength of feeling about their importance, a shortlist of medicines was identified for further investigation.

2.2. Literature review

A review of academic and grey literature was conducted to identify data relating to each of the shortlisted medicines identified from the qualitative analysis. Data were extracted for estimates of health and economic benefit witnessed in the UK for each medicine. Data from published literature were complemented with other publicly available data. Benefits were broadly defined. In terms of health outcomes, we extracted data on the prevalence and incidence of disease, disease-specific mortality, and quality of life improvements. Economic and wider societal impacts of the new medicines were also considered with respect to productivity, health service efficiency, and demographic indicators, as applicable. We sought to identify the best available data to obtain estimates for each medicine. Our analyses also identified where data availability is poor, to inform future research.

We anticipated that older medicines are not likely to have as large an evidence base as more recently developed medicines. This is because trial methodology and regulatory requirements for new medicines have changed dramatically since the inception of the NHS, with an increasing need for evidence production. More recently, real world evidence on the impact of medicines has been generated. The relatively recent establishment of the National Institute for Health Research (NIHR) and the National Institute for Health and Care Excellence (NICE), and growth in the pharmaceutical sector, have significantly increased the supply and demand for heath research. Nevertheless, older medicines with well-understood clinical characteristics that play an important role in the NHS may still lack evidence. Therefore, where necessary, our review targeted disease-specific (rather than medicine-specific) literature and data in order to inform inferences about the impacts of new medicines.

3. RESULTS

3.1. List of medicines

Twelve individuals were invited to interview, of which four did not respond. We conducted eight interviews – two face-to-face and six by teleconference – with leading figures with scientific, clinical, practicing, academic, and regulatory experience in the context of new medicines in the UK.

Data saturation was reached, with no further important medicines identified in the final interviews. In order to maintain interviewees' anonymity, characteristics of individuals are not reported here. Interviewees were currently or previously employed by the NHS, the Medicines and Healthcare products Regulatory Agency (MHRA), NICE, universities, or non-academic research institutions, and some were retired. Several interviewees had been employed in industry at some point in their career. Medical fields and specialties of expertise in the group included cardiology, gastroenterology, general practice, infectious disease, paediatrics, psychiatry, respiratory medicine, and surgery.

From the interviews, 37 medicines or groups of medicines that have been introduced during the history of the NHS were identified as having had an important impact on people's health or the economy in the UK. The medicines are shown in Figure 1.

Figure 1. Medicines timeline by decade of introduction (long-list)

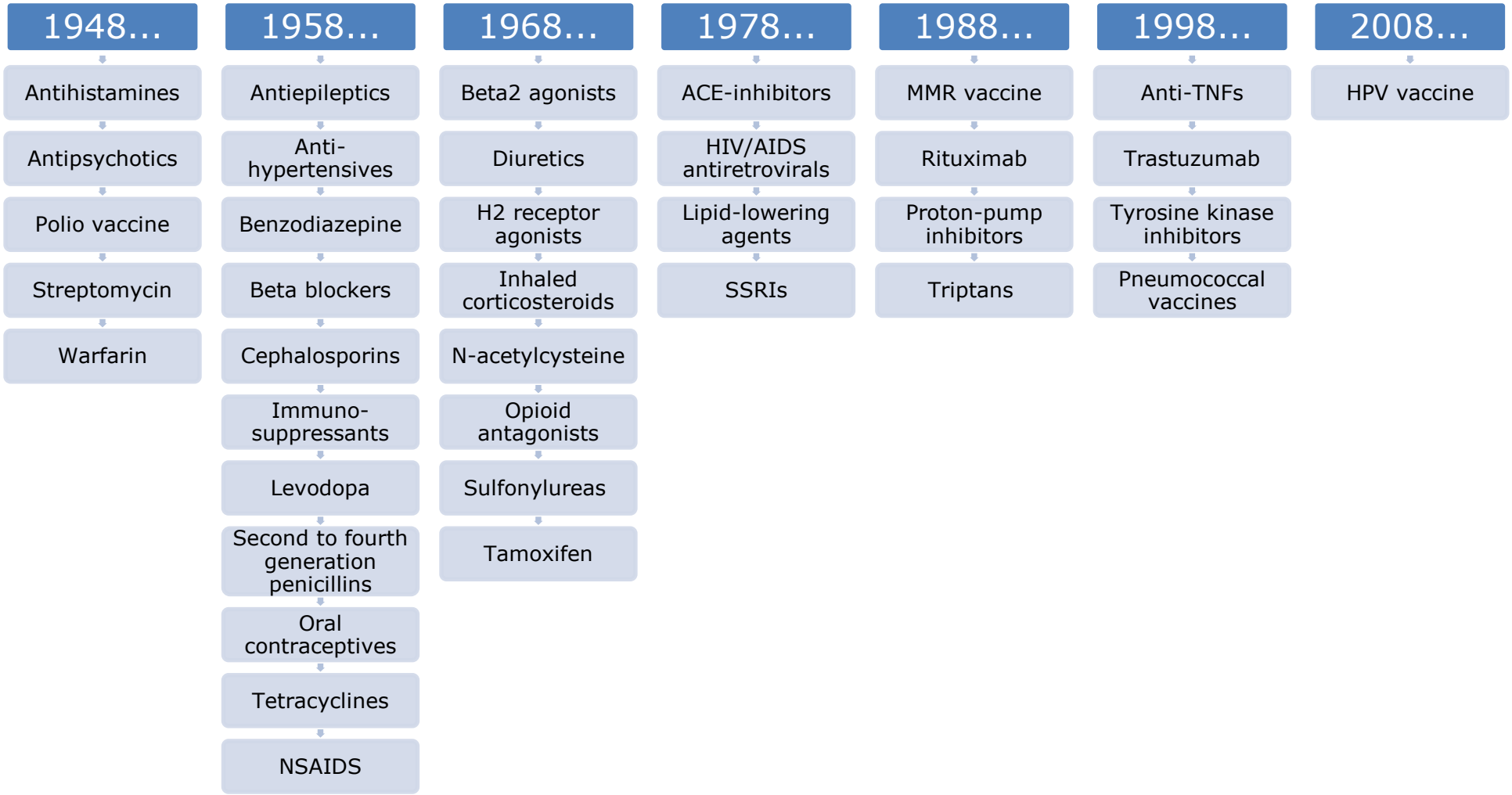


Table 1. Important medicines (shortlist)

Medicine	Year of launch	Manufacturer/Licensee	WHO 'Essential Medicine'?	Price per dose (approximate)[1]	Number of interviewees citing
Chlorpromazine	1953	Laboratoires Rhône-Poulenc (France)	Yes	£1.20	4
Polio vaccine	1955	University of Pittsburgh (USA)	Yes	£6.50	2
Oral contraceptives	1961 (mestranol/ noretynodrel)	Searle (USA)	Yes	£0.03	4
Second to fourth generation penicillins	1961 (ampicillin)	Beecham (UK)	Yes	£5.97	5
Beta blockers	1965 (propranolol)	ICI Pharmaceuticals (UK)	Yes	£0.02	6
Beta2 agonists	1969 (salbutamol)	Glaxo (UK)	Yes	£0.01	5
Tamoxifen	1972	ICI Pharmaceuticals (UK)	Yes	£0.08	3
Immunosuppressants	1983 (cyclosporin)	Sandoz (Switzerland)	Yes	£0.30	4
HIV/AIDS antiretrovirals	1987 (zidovudine)	Burroughs-Wellcome (USA)	Yes	£2.22	6
MMR vaccine	1988	Merck (USA)	No (separate vaccines)	£7.64	3

[1] Source: BNF (Joint Formulary Committee, 2018)

This long-list of medicines does not include medicines that were mentioned by interviewees that were not clearly specified as being important, or for which interviewees were not confident of their importance. It was also noted that some of the most important medicines used in the NHS over the last 70 years are those that were available before 1948, particularly vaccines such as those for diphtheria, tetanus and whooping cough. However, these were acknowledged as being beyond the remit of this study. The distribution of important medicines through time, as shown in Figure 1, was as anticipated. That is, the cumulative impact of medicines grows over time and therefore it is unlikely that newer medicines will have been available for a sufficient time to be considered to have had – relative to older medicines – the greatest impact over a 70-year period.

From the interviews, ten new medicines introduced in the NHS in the last 70 years were identified as being most important. These were selected on the basis of the frequency that they were cited by interviewees and the strength of feeling about the magnitude of their positive impact in the NHS. Table 1 lists details for the shortlist of medicines.

3.2. Quantitative evidence

3.2.1. Chlorpromazine

Chlorpromazine was the first antipsychotic, synthesised in 1951 and first used in the NHS in 1954. It is seen as fundamental in the 'psychopharmacological revolution' and paved the way for deinstitutionalisation and community-based care for people with mental illness, as set out in the 1959 Mental Health Act. BMJ readers identified chlorpromazine as a 'Medical Milestone' and the drug was described as a kind of "psychic penicillin" (Turner, 2007).

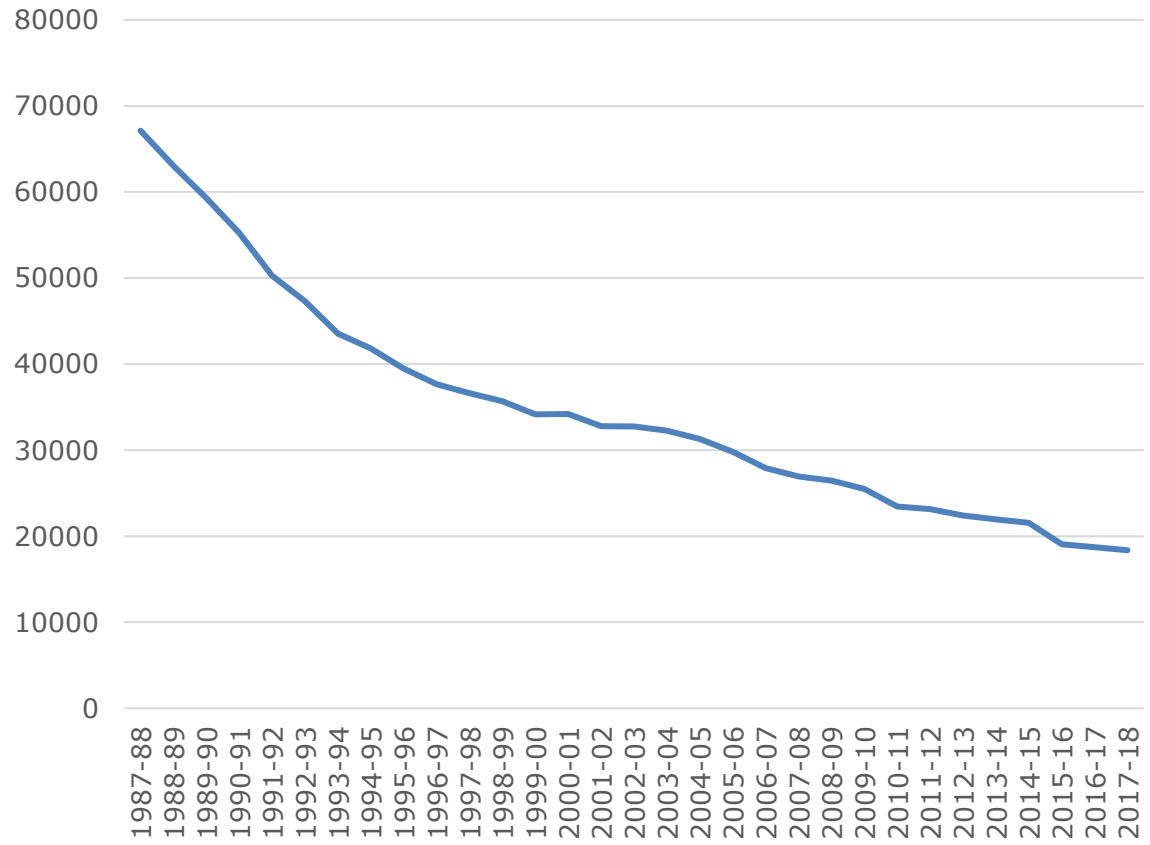
As identified by interviewees in our study, much of the importance of chlorpromazine derives from the fact that it gave rise to all modern antipsychotic and antidepressant medications. Notably, despite being the oldest medicine in our shortlist, it is still included in the WHO Model List of Essential Medicines (World Health Organization, 2017).

Chlorpromazine has primarily been used in the treatment of schizophrenia. In England and Wales, around 220,000 people are diagnosed with schizophrenia (National Institute for Health and Care Excellence, 2014). A Cochrane systematic review of 50 years' worth of randomised controlled trials of chlorpromazine for schizophrenia demonstrated that the medicine promotes a global improvement (Adams et al., 2014). However, because chlorpromazine is a 'benchmark' medicine for schizophrenia, and because it has been widely used for more than 50 years, there is limited evidence of its overall impact or the cost implications of its use.

Interviewees identified early antipsychotics, particularly chlorpromazine, as having had a major economic impact in several ways. Antipsychotic medication was cited as having alleviated agitation on hospital wards, which facilitated more effective and less costly health care. The medicines were also seen as having enabled community-based care to replace hospital-based care in many situations. Both of these features could serve to reduce NHS expenditure on patients with psychosis. In the early 1960s, chlorpromazine facilitated the closure of asylums. Subsequent developments have enabled this trend to continue. Between 1987 and 2017, overnight mental health beds have fallen by 73% (NHS England, 2018), as shown in Figure 2.

A broader societal economic impact was also cited with respect to people with mental health problems being able to continue to work where they would not have been able without medication.

Figure 2. Average daily available beds (mental illness)



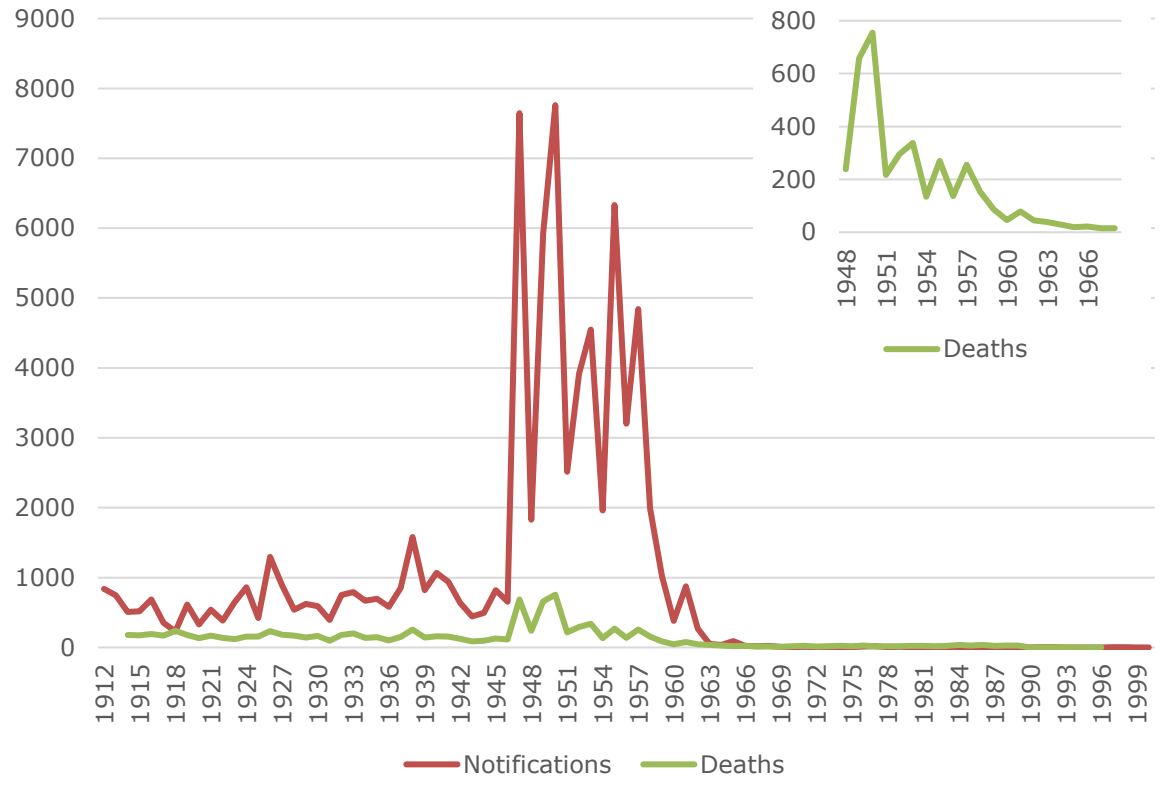
Source: NHS England (2018)

3.2.2. Polio vaccine

All interviewees made reference to vaccines as being important. The first major vaccination programme implemented during the history of the NHS, that was deemed to have had an important impact, was the polio vaccine.

In 1955, the NHS facilitated the successful co-ordination of a poliomyelitis vaccination programme in the UK. However, problems in the supply chain of the vaccine prevented full extension of the programme until 1958 (Lindner & Blume, 2006). By the end of that year, 6.4 million people had been inoculated and – as shown in Figure 3 – the number of polio cases and deaths in England began to rapidly decline. By 1966, the incidence rate had fallen below 1 in every 1 million and polio has been effectively eradicated in the UK. If the number of deaths from Polio in 1958-2018 had equalled the 1914-1958 average, there would have been more than 10,000 additional deaths in England due to polio.

Figure 3. Incidence rates of polio in England



Source: Post-Polio Health International (2018)

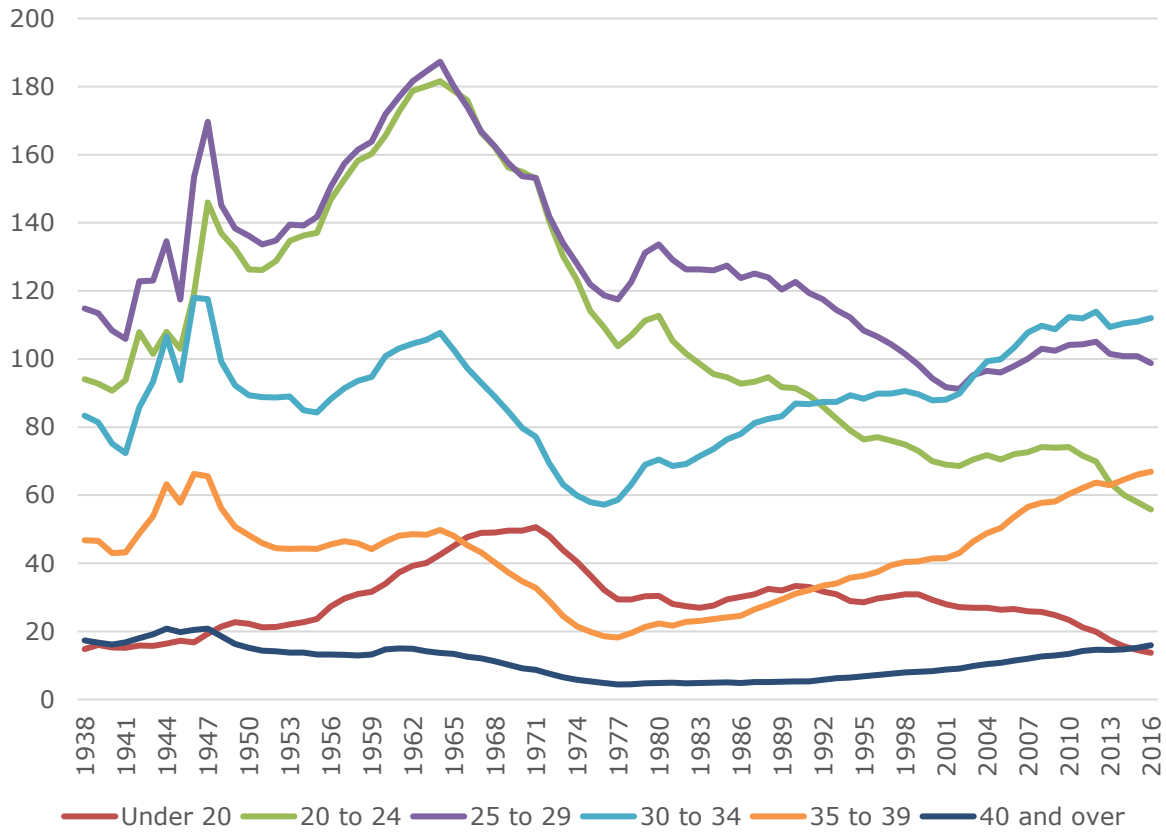
3.2.3. Oral contraceptives

The contraceptive pill is a medical development with perhaps the greatest 'non-medical' consequences (Djerassi, 2007). It was recently identified as one of the '50 things that made the modern economy' in a book by the economist Tim Harford (Harford, 2017). 'The pill' was one of the first medicinal products to be taken on a daily basis by millions of healthy people, creating new dynamics in the consideration of the risks and benefits of pharmaceutical products.

Oral contraception was identified by interviewees as having had an important health, economic, and broader social impact in the UK. The contraceptive pill became widely available in the UK in 1961. This facilitated a sharp decline in the number of women in England and Wales giving birth before the age of 30, as shown in Figure 4.

After being on an upward trajectory throughout the 1950s and early 1960s, the number of births to teenage women has steadily declined since 1970. This is likely to have reduced the incidence of preterm delivery and stillbirth (Smith & Pell, 2001).

Figure 4. Live births per 1,000 women in age group



Source: Office for National Statistics (2017)

3.2.4. Second to fourth generation penicillins

Despite current concerns about antimicrobial resistance and overuse of antibacterial agents, antibiotics are regularly cited as one of the most important developments in the history of medicine. The first antibiotic – penicillin – was discovered in 1928 and used in the UK before the introduction of the NHS, though the NHS facilitated its widespread adoption in the UK. Since 1948, new generations of penicillins have been developed and introduced. In particular, interviewees identified ampicillin, amoxicillin, and flucloxacillin as being (collectively) important.

Interviewees identified a variety of ways in which these new medicines have improved mortality and morbidity associated with infections, and there are many indications for their use. A key role for these more modern penicillins has been in surgery.

Given the numerous uses of penicillins, it is difficult to summate their impact. We found no evidence on the overall impact of modern penicillins on health and economic outcomes in the UK.

3.2.5. Beta blockers

Beta blockers were developed in the 1960s by Sir James Black, who was subsequently awarded the Nobel Prize in Medicine for the discovery. Propranolol – the first beta blocker – was developed in the UK and is now included in the World Health Organization's List of Essential Medicines.

With high rates of mortality and morbidity, heart failure is a serious and growing health problem in the UK. In developed countries, 2-3% of the population is estimated to have heart failure (Cowie et al., 1997), which corresponds with high rates of hospitalisation – around 120,000 per year (Parameshwar et al., 1992).

There is strong evidence that patients randomly assigned to receive beta blockers experience a relative risk reduction in mortality of around 35%, with an absolute difference in mortality rates of around 5% (Shibata et al., 2001). To avoid one death, on average, requires the treatment of 20 patients for approximately 12 months.

Hospitalisation is the major source of expenditure due to heart failure in the NHS (Stewart et al., 2002). If medicines that reduce mortality and morbidity associated with heart failure can help reduce hospitalisations, then the net budgetary impact of these medicines should be positive. A systematic review by researchers in the UK found that an admission for heart failure could be avoided for every 16 patients receiving a year of treatment with beta blockers (Shibata et al., 2001). Propranolol is now available as a generic medication, at very lost cost to the NHS (Joint Formulary Committee, 2018).

3.2.6. Beta2 agonists

Anti-asthma agents were identified by a majority of interviewees as being some of the most important developments of the last 70 years. While some medicines for asthma, such as long-acting beta2 agonists, have caused controversy, the original beta2 agonist – salbutamol – has remained free of such claims (Bryan, 2007). Beta2 agonists like salbutamol work by opening up airways in the lungs, relieving the symptoms of asthma and chronic obstructive pulmonary disease (COPD). Salbutamol was developed in the 1960s at the Allen and Hanburys laboratory by a team led by David Jack.

In the UK in the mid-1960s, for every 100,000 people aged 15-44, around three people died because of asthma (Ross Anderson et al., 2007). A decade later, that rate had fallen below one per 300,000. This shift can be attributed in part to the introduction of salbutamol.

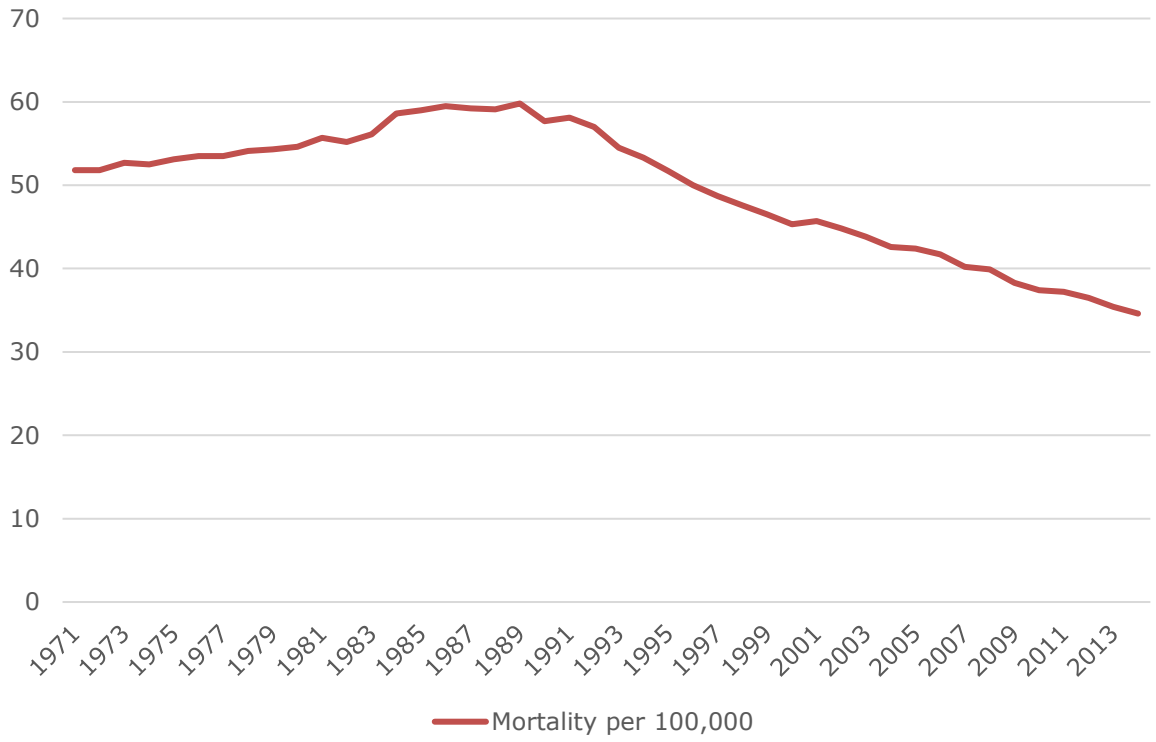
In accordance with the high level of deaths from asthma in the 1960s, hospital admissions due to asthma increased dramatically in all ages groups from the early 1960s to the early 1970s (Ross Anderson et al., 2007), after which the rate of hospitalisations levelled-off for adults. The cost of a salbutamol inhaler – with 200 doses – is now around £1.50 for the NHS (Joint Formulary Committee, 2018).

3.2.7. Tamoxifen

Breast cancer care has undergone major changes over the history of the NHS, including surgery, radiotherapy, hormonal and cytotoxic treatment, and screening by mammography. First available in the UK in 1972, tamoxifen was cited by some interviewees as a key development in breast cancer care with major health impact. The availability of the medicine was part of the justification for the introduction of a national screening programme in 1988, after which breast cancer mortality rates declined significantly, as shown in Figure 5.

A synthesis of data from 20 trials demonstrated that tamoxifen can safely reduce 15-year risk of breast cancer recurrence and death (Early Breast Cancer Trialists' Collaborative Group, 2011). Between 1987 and 1997, annual breast cancer deaths in the UK fell by 22% for 20-69 year-olds and by 12% for 70-79 year-olds (Peto et al., 2000).

Figure 5. Breast cancer mortality rates in the UK



Source: Cancer Research UK (2018)

3.2.8. Immunosuppressants

Immunosuppressive medications facilitated successful organ transplant in the 1960s, with azathioprine. The first kidney transplant took place in Edinburgh in 1960. In 1968, Britain's first heart transplant was carried out in London, but the death of this patient – and failure of subsequent transplants – meant that few were carried out over the next decade. A breakthrough for modern transplant surgery was in 1983, with the introduction of cyclosporin. The first successful heart-lung transplant in the UK was conducted in 1983; 1985 saw Britain's youngest liver transplant patient; and in 1986 the world's first liver, heart and lung transplant was successfully completed. Numerous developments have been made over the years, with many new antirejection medications introduced for transplant surgery in the NHS, such as mycophenolic acid.

Few data exist regarding the effectiveness of azathioprine, which has been replaced with cyclosporin in many contexts following major studies that demonstrated an improvement in 1-year graft survival from around 50% to between 70% and 90% (Taylor et al., 2005). Three major studies demonstrated that mycophenolic acid reduced first-year biopsy proven graft rejection to around 17%, from around 41% in patients with placebo or azathioprine (Taylor et al., 2005).

As identified by interviewees, new developments in immunosuppressive agents can reduce the burden on the health service by reducing the rate of transplant rejection (Taylor et al., 2005), which otherwise leads to further hospitalisation and health service use.

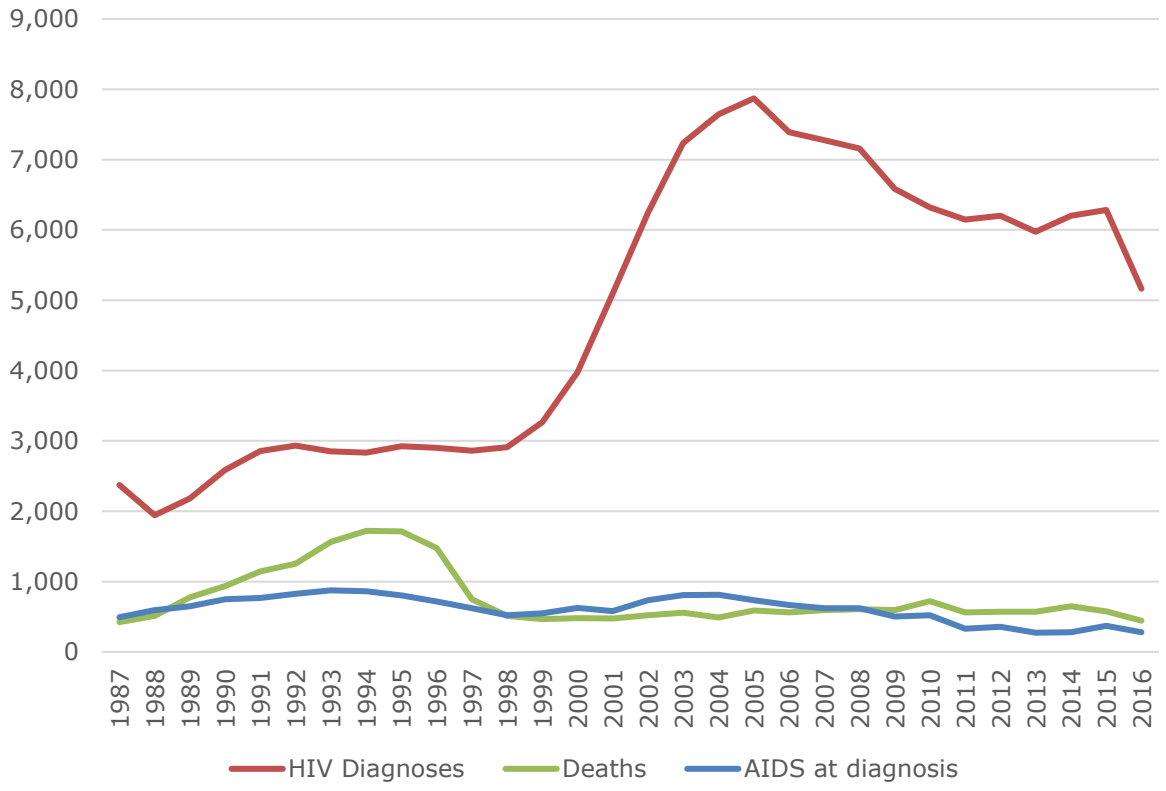
3.2.9. HIV/AIDS antiretrovirals

Zidovudine was the first treatment for human immunodeficiency virus (HIV). Interviewees pointed to zidovudine and other antiretroviral treatments for HIV as having prevented an acquired immune deficiency syndrome (AIDS) pandemic that could have overwhelmed the NHS. The UK launched its first AIDS health campaign in 1986, and zidovudine became available the following year. Figure 6 shows that, despite dramatic growth in the number of diagnoses from 1987 to 2005, the number of deaths in 2005 was far lower than the number of deaths at its peak in 1994.

Antiretroviral treatment has been used to reduce vertical transmission rates for HIV, reaching 97% of live births in 1998. In combination with caesarean section, antiretroviral treatment reduced the risk of transmission from 32% to 4%. Vertical transmission rates from HIV infected women to children reached 19.6% in 1993, and fell to 2.2% in 1998, with the proportion of infected children developing AIDS within 6 months falling from 18% to 7% (Duong et al., 1999).

Subsequent developments in the treatment of HIV, including combined antiretroviral therapy (cART), have achieved major gains in morbidity and mortality. cART has been shown to reduce mortality by 50% (The HIV-CAUSAL Collaboration, 2010). Data from the UK demonstrate that the rate of survival following HIV seroconversion has improved over time (Ewings et al., 2008).

Figure 6. HIV/AIDS diagnoses and deaths in England and Wales

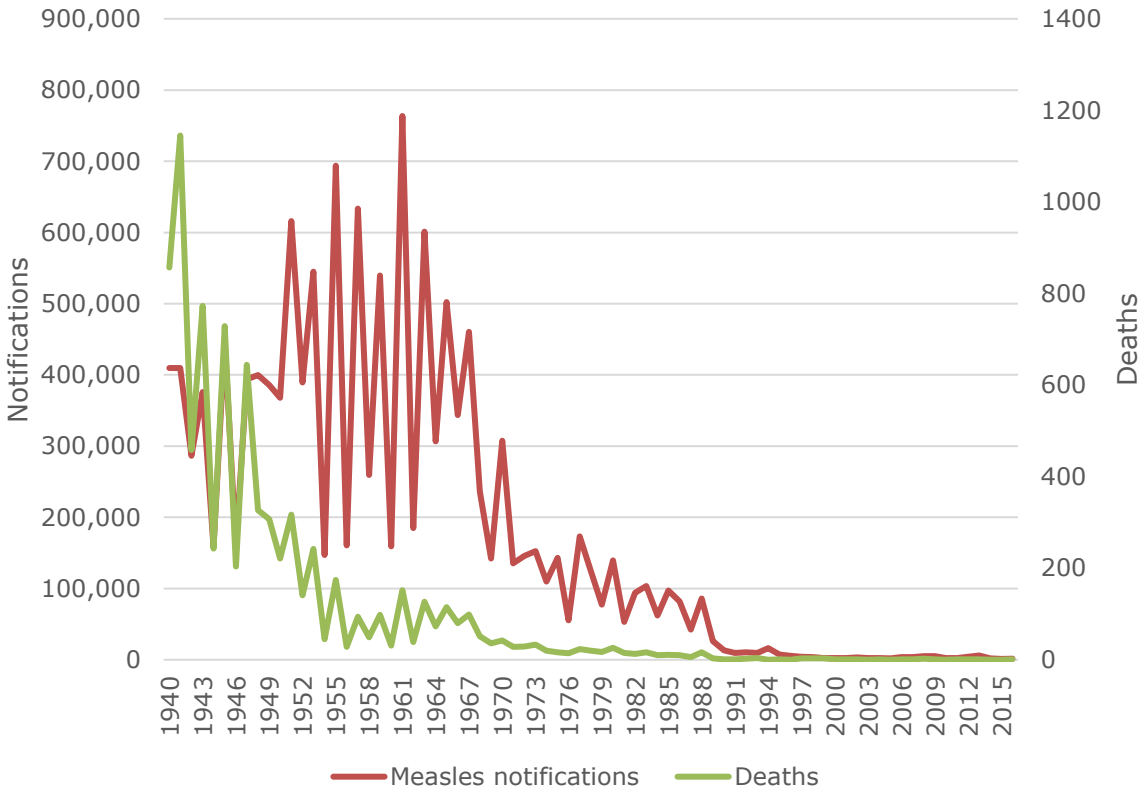


Source: Public Health England (2017b)

3.2.10.MMR vaccine

In 1948, there were almost 400,000 cases of measles in the UK, and 327 people died. In 1968, a measles vaccine was introduced and the number of cases and deaths fell dramatically. However, in 1987, the year before the MMR vaccine was introduced, there was still a high number of cases (42,000) and six deaths, as shown in Figure 7. 1994 was the first year with no deaths from measles in the UK and infection with the disease could no longer be considered "as inevitable as death and taxes" (Babbott & Gordon, 1954). By 2015, the number of cases had fallen below 1,200.

Figure 7. Measles notifications and deaths in England and Wales



Source: Public Health England (2017a)

3.3. Themes on the impact of medicines

Seven themes arose from the interviews, each representing a factor that has played an important role in determining the impact of new medicines: i) the value of innovation, ii) complementarity and spillovers, iii) substitution, iv) policy, v) evidence, vi) understanding, and vii) collaboration. Each of these themes was discussed by several interviewees, with some providing examples that related to multiple themes.

3.3.1. The value of innovation

The interviewees consistently discussed the nature of innovation and the ways in which it can bring value to patients beyond the direct benefit associated with a specific development. Broadly speaking, the interviewees judged there to be value in developing

new medicines that may not have immediate commercial value or provide large-scale benefits to the population. For example, one interviewee stated that:

> "The drugs themselves may not be used for enormous numbers of patients, but the principle that we learnt from those drugs is really important."

Innovations in cardiovascular medications were especially highlighted, with one interviewee commenting that:

> "We learn so many lessons from the cardiovascular field which are applicable to other areas."

A key idea relating to innovation was that the first medicine in its class may or may not bring important benefits to patients through its use, but that often it is the combined impact of its derivatives and developments that it enabled that constitute important advances in health care. This was primarily discussed in the context of cardiovascular medicines and antipsychotics. One interviewee stated that:

> "So, it is not the first drug in the field which makes the biggest impact. People learn from that and it goes on to the second drug in the field and subsequent ones and that in itself is a very important lesson."

When a medicine is found to work, it stimulates further research about the mechanisms of action that tend to give rise to the refinement of more targeted therapies. This step-by-step or incremental approach to innovation was characterised by several interviewees.

There is also a social element to the multiplier effect by which innovation can breed innovation. Where new medicines in a particular field have been found to bring benefits to patients, pharmacologists are likely to be attracted to work in that area.

Further supporting the benefit of incremental innovation to patient care was the potentially stifling nature of breakthrough innovations. For example, one interviewee noted that the effectiveness of chlorpromazine could have meant that researchers did not follow alternative development leads.

It can also be difficult to predict exactly how a new innovation will be used, and the means by which it will create patient benefit. Interviewees raised several examples where new medicines have been repurposed or have been accidentally found to be more effective in an unintended condition. This can be particularly important where illnesses have emerged, either as entirely new or as affecting a significant section of the population where they hadn't previously.

3.3.2. Complementarity and spillovers

All interviewees expressed – in a variety of respects – the importance of considering the value of new medicines in a wider context. There were three mechanisms identified: i) complementarity between new medicines and existing medicines, ii) complementarity between new medicines and non-pharmaceutical care, and iii) spillovers in the impact of medicines.

Several interviewees expressed the importance of new medicines being used in combination with existing medicines, and that this can increase the value of both. One interviewee noted that:

> "All the drugs which have come along after [thiazide diuretics] have used diuretics as an add-on to improve their efficacy."

However, the challenge of polypharmacy and drug interactions was also highlighted in this context.

New medicines also complement non-pharmaceutical care. A prime example forwarded by interviewees was for zidovudine in the treatment of HIV and AIDS. One interviewee stressed that it was the combination of health advice, drugs, and condoms that together made a difference to people with HIV/AIDS.

Another key example of new medicines complementing non-pharmaceutical health care is in surgery, where new medicines have dramatically shifted the benefit to risk ratio. One interviewee characterised new penicillins as being 'game-changers' in surgery in the 1960s and 1970s, when surgical outcomes improved dramatically while surgical techniques remained largely unchanged. Furthermore, in the context of cancer, new medicines have facilitated more effective multimodal therapy. Interviewees identified the ability of new medicines to reduce the size of tumours such that patients can go from being inoperable to being operable, with improved survival.

Drug eluting stents and combinations of medicines and devices were highlighted as important. There are also examples where the impact of new medicines is almost entirely dependent on peripheral developments. Delivery mechanisms, in particular, were presented as a crucial facilitator in the impact of medicines. In the context of complementarity, the most important example suggested by interviewees was the case of metered-dose inhalers for asthma:

> "I think the development of those devices has been quite important and has probably saved quite a lot of people's lives."

New medicines are not introduced in a vacuum with one illness and one treatment. Patients can exhibit a wide range of symptoms with a variety of causes and can also be taking multiple medications, creating the possibility for spillover effects. Sometimes this reality can undermine the impact of new medicines. However, sometimes unintended consequences can arise that are positive. Two examples presented by interviewees were rheumatic heart disease, which one interviewee suggested has largely vanished due to the wide use of antibiotics, and catatonia, which may have been inadvertently addressed by the wide use of benzodiazepines.

One interviewee warned about the potential for new medicines – especially where evidence is incomplete – to lead to the creation of new and costly infrastructure such as screening programmes. This may undermine the cost-effectiveness of otherwise inexpensive new medicines.

3.3.3. Substitution

Substitution was a key driver of the economic impact of medicines. This could extend beyond substitution between medicines and was raised particularly in the context of surgery and mental health care.

Several interviewees identified antipsychotic medications as facilitating the closure of hospitals by substituting hospital-based care for community-based care. Though some interviewees characterised this substitution as having been taken too far by decision-makers.

With respect to surgery, interviewees identified the substitution to pharmacotherapy in the context of peptic ulcers, whereby surgery for peptic ulcers is now rarely necessary, with pharmacotherapy as a less costly and more effective alternative.

3.3.4. Policy

All interviewees identified policy as being important in determining the impact of medicines in some respect. Major policy endorsements could be a prerequisite for medicines to have impact. This was deemed especially true for vaccinations, and the polio vaccine in particular, for which there was a commitment from the government to provide it universally.

Another mode by which policy can enhance the impact of medicines is by facilitating access. For example, medicines becoming available over the counter was identified as being crucial in the use of medicines in certain contexts. Policies relating to quality assurance were also highlighted as having been critical in the impact of medicines. For example, one interviewee described the importance of advances in packaging and production standards in the NHS:

> "we forget that before the [National] Health Service, when you got a tablet, [the dose] might well be 50% out… I think the whole packaging and the production of pills and tablets is really quite an important change to the benefit."

Examples were also provided for policy arrangements that restrict the potential for new medicines to have a positive impact. Several interviewees pointed to the speed of regulatory processes to ensure that effective medicines are available and that dangerous medicines are withdrawn:

> "We are still taking too long to withdraw drugs that are dangerous and that are causing serious adverse reactions. That I think is a regulatory problem."

3.3.5. Evidence

The availability of good evidence was identified as having become a prerequisite for medicines to achieve their full impact. This was less true in the early days of the NHS.

Large clinical trials were argued to facilitate rapid adoption, while uptake for medicines with limited evidence can be patchy and gradual. The impact of new medicines can be limited in contexts where evidence is lacking. Several interviewees discussed this challenge in the context of children. A lack of evidence for the use of medicines in children could mean that children are not able to experience the same level of benefit as adults:

> "The problem in children is that there are very few trials in children because of ethical difficulties and practical difficulties. Not all but a huge amount of the information that comes for treating children is based on treating adults… In the absence of such evidence, you just do not know and that means that probably children are not getting as good a deal as adults."

Increasingly, epidemiological studies and real-world evidence are seen to be playing an important role in supporting adoption where trial evidence is limited. Real-world evidence was characterised as being necessary but not sufficient. It was suggested that evidence needs to be identified early on:

> "Without careful studies, I think in the pre-marketing phase you may miss serious adverse reactions that you are now relying on picking up after marketing."

There was also a suggestion that evidence can be skewed, which can harm patients:

> "… there's been heavy pressure on people not to look at the harms, not to look at things that may be going wrong, and part of the problem with not looking at

> these things is if you don't look at what may be going wrong you can't put it right, so things tend to just accumulate."

3.3.6. Understanding

A major barrier to the impact of medicines is the level of understanding amongst patients, clinicians, and regulators.

With respect to clinicians, the work of NICE – particularly clinical guideline development – was recognised as being an essential driver in facilitating better understanding and of great value to the effective use of medicines in England.

Several interviewees identified the pervasiveness of a general assumption that new medicines provide more benefit than harm, and that this can be problematic. Patients' demand for treatments does not always align with new medicines having a positive impact. One interviewee pointed to the example of trastuzumab for early breast cancer, which patients demanded despite an unfavourable risk-benefit ratio.

Conversely, interviewees also identified a tendency to overstate the risks of medicines. Some interviewees implicated the media in this, suggesting that it was common for the news media to sensationalise potential harms and to encourage patients to reject beneficial medicines:

> "if you pick up [some newspapers], all that they are saying/all that they are interested in is the risk."

Interviewees suggested that this played an especially important role in the context of vaccines, where public attitudes are swayed by individuals and the media. This was most notably observed with respect to the "health scares" associated with use of the MMR vaccine:

> "I think the media has had a huge effect. The way the media has treated health scares has had a huge effect on the uptake of vaccination."

There can also be more general misunderstandings about the nature of new medicines, which can skew perceptions of the benefits and risks of treatments:

> "[Patients have] heard about anabolic steroids and the hazards of those – body builders and all that – and they link them to steroids that we use for asthma."

Several interviewees pointed to patients' level of understanding as a key barrier or facilitator to the impact of medicines, and that this especially operated through levels of adherence:

> "if you ask me, 'What do you think the biggest problem in therapeutics is today?', my answer to that is 'patient adherence and patient compliance.'"

> "Because they don't have any symptoms from their hypertension until it is too late – until they have had their heart attack or their heart failure – they don't really have any symptoms."

> "If you have, like, cyclosporin or you have HIV, you do need to take [medication] every single day, year in, year out, and that is not understood by many people."

Patients often do not witness the benefits of new medicines, or at least do not witness the counterfactual of life without the medicines. Thus, new medicines may appear to patients to be having no benefit. New medicines may also create inconveniences for

patients, such as blood pressure measurements for hypertensive patients, which make them seem both ineffective and inconvenient.

3.3.7. Collaboration

Collaboration – either direct or indirect – was presented as an important mechanism in the impact of new medicines. This collaboration could operate between industry and the NHS, universities, and regulators. One interviewee suggested that:

> "The NHS itself does not generate new medications, it does not of itself do the research that supports the medications, but it may facilitate the use of the medicine by facilitating clinical trials, for example, within its boundaries."

This was characterised mainly as individual clinicians and pharmacologists collaborating with industry partners to facilitate the development of effective new medicines and to organise their provision. One interviewee identified the creation of the NIHR as an important development in the capacity for collaboration and suggested that it could increase the impact of medicines.

Another form of collaboration forwarded by several interviewees was that between universities and industry. One interviewee suggested that universities were "just as important", but other interviewees suggested that the majority of collaboration operates indirectly through co-dependence upon research in both settings.

A further important form of collaboration was highlighted as taking place between industry and regulators, such that regulators support the process of drug development and introduction.

In contrast to collaboration, competition received some discussion, but did not arise as a key theme. Interviewees suggested that competition could drive cost savings where alternative devices or delivery mechanisms were created, such as in the context of asthma treatment.

4. DISCUSSION

It is a challenge to understand the impact of medicines in the history of the NHS. New medicines have been introduced in an ever-changing service with shifting social and environmental influences on health and health care. This study has considered a selection of new medicines identified by experts as being particularly important in the UK health economy. Furthermore, several themes arose from qualitative interviews that can inform future research and policy-making.

Interviewees consistently identified new medicines – even those for which they were confident of a major positive impact – as having diffuse health and economic implications that are difficult to quantify. This view was reinforced by the lack of evidence on the cumulative benefit of specific medicines in the NHS. For the medicines considered in this study, we did not find any studies that estimated an overall cumulative impact of the medicine over time. Research of this kind is warranted in order to understand the true impact of medicines in the NHS. As emphasised by interviewees, the creation of evidence – both before and after the introduction of new medicines in the NHS – is a necessary condition for medicines to have a positive impact.

The medicines specified by interviewees were characterised as being important in different ways. Some medicines were considered important because of their capacity to reduce preventable deaths, others because they improved patients' quality of life, and

others because of their impact on the NHS, the wider economy, or society. This highlights the importance of adopting a broad understanding of value and demonstrates the challenge of making comparisons of value between different medicines.

The themes identified in our interviews highlight a variety of ways in which policy-makers can facilitate positive impact from new medicines. Improving public, patient, and clinician understanding of new medicines was identified as being of critical importance. Interviewees stressed the importance of improving public understanding, suggesting that current provision is inadequate and that this is reflected in poor patient adherence, which restricts the positive impact of medicines.

All interviewees discussed the nature of innovation and the various ways in which new medicines can bring benefit to patients. However, all emphasised the importance of generating evidence and developing effective regulatory frameworks in order to enhance the impact of new medicines. Real-world evidence can expedite the identification of new medicines' spillover effects and the nature of any complementarity and substitutability within the health service. Innovation can be strengthened by cross-sector collaboration between researchers and with clinicians, which can expedite new developments.

There is no doubt that new medicines have had a major impact on health outcomes for NHS patients, and that they have had important consequences for the UK economy. As discussed by our interviewees, these benefits are difficult to quantify, though it is possible if looking across broad disease areas and returns to research funding (Glover et al., 2014, 2018). We found the available evidence for the cumulative impact of new medicines to be lacking. This is likely due to the complexity of the mechanisms by which medicines bring benefits to patients.

A general theme relating to impact on the NHS, not captured by the evidence, arises as a consequence of the lifecycle of the medicines market. All of the medicines included in the study have been available for at least thirty years and now face generic competition. Mechanisms in place to deliver market efficiencies help to ensure that, where medicines face generic competition, the NHS can procure at prices lower than those paid when the medicine was still patent-protected.

REFERENCES

Adams, C. E., Awad, G. A., Rathbone, J., Thornley, B., & Soares-Weiser, K., 2014. Chlorpromazine versus placebo for schizophrenia. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD000284.pub3

Babbott, F. L., & Gordon, J. E., 1954. Modern measles. *The American Journal of the Medical Sciences*, 228 (3), 334–361.

Bryan, J., 2007. Ventolin remains a breath of fresh air for asthma sufferers, after 40 years. *The Pharmaceutical Journal*, 279, 404.

Cancer Research UK, 2018. Breast Cancer (C50): 1971-2014.

Cowie, M. R., Mosterd, A., Wood, D. A., Deckers, J. W., Poole-Wilson, P. A., Sutton, G. C., & Grobbee, D. E., 1997. The epidemiology of heart failure. *European Heart Journal*, 18 (2), 208–225. https://doi.org/10.1093/oxfordjournals.eurheartj.a015223

Cutler, T., 2003. Dangerous yardstick? Early cost estimates and the politics of financial management in the first decade of the National Health Service. *Medical History*, 47 (2), 217–238.

Djerassi, C., 2007. The pill: emblem of liberation. *BMJ*, 334 (suppl_1), s15–s15. https://doi.org/10.1136/bmj.39051.582546.94

Duong, T., Ades, A. E., Gibb, D. M., Tookey, P. A., & Masters, J., 1999. Vertical transmission rates for HIV in the British Isles: estimates based on surveillance data. *BMJ (Clinical Research Ed.)*, 319 (7219), 1227–1229.

Early Breast Cancer Trialists' Collaborative Group, 2011. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *The Lancet*, 378 (9793), 771–784. https://doi.org/10.1016/S0140-6736(11)60993-8

Ewings, F. M., Bhaskaran, K., McLean, K., Hawkins, D., Fisher, M., Fidler, S., … UK Register of HIV Seroconverters, 2008. Survival following HIV infection of a cohort followed up from seroconversion in the UK. *AIDS (London, England)*, 22 (1), 89–95. https://doi.org/10.1097/QAD.0b013e3282f3915e

Glover, M., Buxton, M., Guthrie, S., Hanney, S., Pollitt, A., & Grant, J., 2014. Estimating the returns to UK publicly funded cancer-related research in terms of the net value of improved health outcomes. *BMC Medicine*, 12 (1), 99. https://doi.org/10.1186/1741-7015-12-99

Glover, M., Montague, E., Pollitt, A., Guthrie, S., Hanney, S., Buxton, M., & Grant, J., 2018. Estimating the returns to United Kingdom publicly funded musculoskeletal disease research in terms of net value of improved health outcomes. *Health Research Policy and Systems*, 16 (1), 1. https://doi.org/10.1186/s12961-017-0276-7

Harford, T., 2017. *Fifty Things that Made the Modern Economy*.

Joint Formulary Committee, 2018. *British National Formulary (online)*. London: BMJ Group, Pharmaceutical Press, and RCPCH Publications.

Lindner, U., & Blume, S. S., 2006. Vaccine innovation and adoption: polio vaccines in the UK, the Netherlands and West Germany, 1955-1965. *Medical History*, 50 (4), 425–446.

Lu, C.-J., & Shulman, S. W., 2008. Rigor and flexibility in computer-based qualitative research: Introducing the Coding Analysis Toolkit. *International Journal of Multiple Research Approaches*, 2 (1), 105–117. https://doi.org/10.5172/mra.455.2.1.105

National Institute for Health and Care Excellence, 2014. *Costing statement: Psychosis and schizophrenia in adults: treatment and management: Implementing the NICE guideline on Psychosis and schizophrenia in adults (CG178)*.

NHS England, 2018. Bed Availability and Occupancy Data – Overnight.

Office for National Statistics, 2017. Births in England and Wales: 2016.

Parameshwar, J., Shackell, M. M., Richardson, A., Poole-Wilson, P. A., & Sutton, G. C., 1992. Prevalence of heart failure in three general practices in north west London. *The British Journal of General Practice : The Journal of the Royal College of General Practitioners*, 42 (360), 287–289.

Peto, R., Boreham, J., Clarke, M., Davies, C., & Beral, V., 2000. UK and USA breast cancer deaths down 25% in year 2000 at ages 20–69 years. *The Lancet*, 355 (9217), 1822. https://doi.org/10.1016/S0140-6736(00)02277-7

Post-Polio Health International, 2018. Incidence Rates of Poliomyelitis in England. Retrieved May 18, 2018, from http://www.post-polio.org/ir-eng.html

Public Health England, 2017.a Measles notifications and deaths in England and Wales: 1940 to 2016.

Public Health England, 2017.b National HIV surveillance data tables. Retrieved from https://www.gov.uk/government/statistics/hiv-annual-data-tables

Ross Anderson, H., Gupta, R., Strachan, D. P., & Limb, E. S., 2007. 50 years of asthma: UK trends from 1955 to 2004. *Thorax*, 62 (1), 85–90. https://doi.org/10.1136/thx.2006.066407

Shibata, M. C., Flather, M. D., & Wang, D., 2001. Systematic review of the impact of beta blockers on mortality and hospital admissions in heart failure. *European Journal of Heart Failure*, 3 (3), 351–357.

Smith, G. C. S., & Pell, J. P., 2001. Teenage pregnancy and risk of adverse perinatal outcomes associated with first and second births: population based retrospective cohort study. *BMJ*, 323 (7311), 476–476. https://doi.org/10.1136/bmj.323.7311.476

Stewart, S., Jenkins, A., Buchan, S., McGuire, A., Capewell, S., & McMurray, J. J. J. V, 2002. The current cost of heart failure to the National Health Service in the UK. *European Journal of Heart Failure*, 4 (3), 361–371.

Taylor, A. L., Watson, C. J. E., & Bradley, J. A., 2005. Immunosuppressive agents in solid organ transplantation: Mechanisms of action and therapeutic efficacy. *Critical Reviews in Oncology/Hematology*, 56 (1), 23–46. https://doi.org/10.1016/j.critrevonc.2005.03.012

The HIV-CAUSAL Collaboration, 2010. The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals. *AIDS*, 24 (1), 123–137. https://doi.org/10.1097/QAD.0b013e3283324283

Turner, T., 2007. Chlorpromazine: unlocking psychosis. *BMJ*, 334 (suppl_1), s7–s7. https://doi.org/10.1136/bmj.39034.609074.94

Wells, N., 1980. *Medicines: 50 Years of Progress 1930-1980*. London.

World Health Organization, 2017. *WHO Model List of Essential Medicines*.

APPENDIX

Impact of medicines interview guide

Thank you for agreeing to take part in this interview. The Office of Health Economics (OHE) has been commissioned by the Association of the British Pharmaceutical Industry (ABPI) to conduct a study on the impact of new medicines in the UK over the last 70 years. This is to coincide with celebrations marking the 70th anniversary of the NHS.

With this interview programme, we aim to identify a list of medicines introduced since the inception of the NHS that are - in the views of experts - particularly important. In a subsequent phase of the study we will collect and collate quantitative data on these medicines.

By important, we mean those medicines that have had the greatest positive impact on the NHS, people's health in the UK, and on the economy more broadly over the last 70 years. We are only interested in 'new' medicines, that is, we are researching medicines that became available to patients in the UK during the NHS's 70-year history.

The views that you express in this interview will be used to develop a series of case studies for these important medicines, supported by evidence-based summaries of their health and economic impact in the UK.

The interview is based on open-ended questions and is structured around three main themes:

A. General perceptions of the impacts of medicines

B. Medicines development through time

C. New medicines in a range of contexts

Before we get started, we will ask if we could record our conversation for note-taking purposes.

Our discussion won't be shared except for in an aggregated form along with other interviewees' responses. However, we'd like to know whether – in principle – you would be happy for OHE or ABPI to contact you for comment, once the findings of the study have been prepared.

Introductory questions

1. Please could you provide a brief overview of your professional experience with respect to medicines introduced in the UK?
2. Has your professional experience focussed on particular medicines or groups of medicines?
3. For which decades of the NHS's history is your knowledge of new medicines greatest?

General perceptions of the impacts of medicines

1. Thinking about your own professional experience, what have been some of the more important medicines introduced to the NHS during your career?
2. What do you believe to have been the single most important breakthrough in the last 70 years, in terms of medicines used in the UK?
    a. Why did you select this medicine?
3. Please can you tell me about the timeline of this medicine? When was it introduced in the NHS?
    a. What was treatment like before this medicine was introduced?
    b. Was it immediately made widely available to patients?
    c. How has its use changed over time?
4. How would you summarise the health impact of this medicine?
    a. What makes this medicine important in your view?
    b. What has influenced the health impact of this medicine
        i. Policy
        ii. Uptake
        iii. Access
5. What do you perceive to be the economic impact of this medicine, whether related to individual patients' lives or the NHS or wider society?
6. Have the impacts you described been accurately described by research?

Medicines development through time

7. Are there any medicines that you would identify as being particularly important that were introduced earlier than [medicine identified as being most important]?
    a. What about the time before your career in working with medicines began?
    b. How about in the 1940s, 50s, and 60s?
8. Please could you tell me about the health and economic impact of these medicines over time.
9. Are there any medicines introduced to the NHS in recent years – say, since the year 2000 – that you believe to have already had a major impact?

New medicines in a range of contexts

10. I'd now like you to try and think outside of your specific field of expertise and about the full range of services provided by the NHS.
    a. Are there any important medicines from the field of [surgery/psychiatry/paediatrics/public health/internal medicine/vaccines]