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Realising the Broader Value of Vaccines in the UK

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Executive Summary

Vaccination programmes are one of the most cost-effective health interventions a health care system can undertake. In many cases they are cost-saving, and the UK has a long-standing track record of offering a world-class national vaccination schedule to tackle vaccine-preventable diseases.

The academic literature suggests that vaccines deliver value beyond narrowly defined clinical effects that are usually the focus of cost-effectiveness analyses to guide decision making on resource allocation under a budget constraint. Beyond health effects, vaccines can have a significant impact on the economics of the health care system or the productivity of a society. Furthermore, many vaccines produce community or health system externalities.

As a result, current health economic evaluations may be underestimating the value of immunisation programmes if the broader value of vaccination is not adequately captured. This can result in a potential suboptimal reimbursement level and hence may impact the pipeline activity in the long run, as it gets harder for innovators to recoup their return on investment.

The following report firstly provides an update on the vaccine pipeline from a UK perspective. Secondly, using a newly developed framework, it shows whether a selected set of vaccines that are currently in phase III development potentially generate value beyond the traditional value dimensions. Finally, the resulting assessment is compared to the current status quo of methodologies used by the National Institute for Health and Care Excellence (NICE) and the Joint Committee on Vaccination and Immunisation (JCVI), the two institutions that effectively regulate the access to therapeutic and preventative vaccines.

Interviews with experts on market access for vaccines and immunisation in the UK (n=5) and globally (n=2) and on regulations for preventative immunisation programmes (n=1) were used to validate or challenge each step.

The results show that preventative and therapeutic vaccines are likely to deliver value beyond health-related quality of life and length of life. Many new vaccinations, for example, have the potential to accrue value by preventing antimicrobial resistance, by generating gains in patient and carer productivity, and by enabling other non-vaccine related interventions that might otherwise not be a safe treatment option. Furthermore, our research indicates that preventative vaccination programmes, which tend to target children, prevent early mortality or long-term disability and have a significant positive effect on productivity.

Formally recognising the broader value of future vaccines is therefore not trivial, nor is it straightforward to achieve. It requires transparent processes, advanced evaluation methodologies and reliable evidence. It also entails the development of novel ideas on how to appropriately reward for value that is generated outside the health care system and therefore beyond the scope of the currently recommended methods for health technology assessment in the UK.

The following recommendations are provided to stimulate those areas where more discussion and research is needed, in order to pave the way towards the recognition of the broader value of future vaccines:

- Find approaches to recognise the productivity value generated outside the health system's perspective
- Recognise the enablement value for non-vaccine interventions and the value in fighting AMR
- Increase transparency and comprehensiveness of value assessment process and stimulate stakeholder engagement
- Proactively steer the generation of high quality & relevant evidence

1 Introduction

The United Kingdom (UK) has a long-standing track record of offering a world-class national vaccination schedule to tackle vaccine-preventable diseases. The first vaccination ever undertaken was done in this country: In 1796, Edward Jenner demonstrated for the first time, using the case of smallpox, that vaccination can create immunisation (Stern and Markel, 2005). Nowadays the national schedule contains more than 15 different vaccination programmes (GOV.UK, 2019), with the most recent version of the universal human papillomavirus (HPV) programme added in 2019.

The vaccines that are part of the UK immunisation schedule to infants, adults and senior citizens (VOX, 2019) are *preventative* vaccines that are administered to otherwise healthy individuals often at a very young age. In addition, an increasing number of *therapeutic* vaccines are being developed, which induce anti-viral immunity to alter the course of disease after infection or disease occurs (Gillespie et al., 2013).

In the UK, market access for both vaccine types is separated. The Joint Committee on Vaccination and Immunisation (JCVI), an independent committee which advises Ministers of Health in the UK on preventative vaccine policy, basically confers the right to the vaccine to the population of England and Wales (Hall, 2010). The assessment of therapeutic vaccines is in the remit of the National Institute for Health and Care Excellence (NICE), which generally applies the same criteria as for other health-related interventions. However, no therapeutic vaccine has been appraised by NICE to date.

Vaccination programmes are one of the most cost-effective health interventions a health care system can undertake. In many cases, they are even cost-saving (Drummond, Chevat and Lothgren, 2007). Preventative vaccination programmes, in particular, are typically rolled out with long-term public health goals in mind and may bear wider economic benefits beyond direct health benefits and medical cost savings (Jit et al., 2015a). If enough people are vaccinated against infectious disease, herd immunity results in what economists call a positive externality – the protection of unvaccinated individuals through a general reduction in the circulation of the disease-inducing pathogen. Furthermore, vaccination may contribute to the objectives of social policy in addition to the goals of the health care system (Luyten and Beutels, 2016). For example, vaccination may support the social integration of minorities if stigmatisation is fuelled by transmissive diseases. It may also enable the achievement of more equitable health outcomes by preventing disease occurrence across different socio-economic groups.

It is therefore likely that vaccines have delivered value beyond narrowly defined clinical benefits and that the vaccine pipeline has the potential to continue to deliver significant and broad value. The UK Government calls for evolving the world-renowned vaccination programme, by further increasing uptake of existing vaccines and through incorporating new ones" (DHSC, 2018b). However, the question arises if, in the presence of scare resources, the current value assessment methods may undervalue the broader benefits of vaccines: The one-size-fits-all-method of cost-effectiveness evaluation (CEA) to assess the value of vaccines correctly, has been questioned by academics as it typically considers only direct health benefits and medical cost savings and does not account for the particularities of vaccines (Jit et al., 2015a).

This following report, therefore, reviews the current state of the vaccine pipeline with relevance to the UK and analyses where future vaccines will deliver broader aspects of value outside the traditional value dimensions. Firstly, we introduce a new value assessment framework that can be used to capture these broader aspects of value. Secondly, we summarise the vaccine pipeline and assess selected future vaccines against the new framework. Finally, we review the current assessment methodologies of relevant regulators in the UK and conclude with recommendations, for creating the

right incentives and value assessments, for policy stakeholders and government decision-makers to realise the potential broader benefits of future vaccines.

2 Methodology

To answer the research questions, a set of specific methods were applied (see Figure 3). First, we developed a value framework that captures the broader value of vaccines based on a targeted review of the literature. In parallel, we present an updated summary of the vaccines pipeline in the UK using data from public and commercial databases. Subsequently, a selection of pipeline vaccines, with particular relevance to the UK, was assessed against this framework. Specifically, we identified the value dimensions where these future vaccines are expected to deliver the greatest value, to the broad dimensions of the framework, based on literature and expert opinions. Finally, the current assessment methodologies and value dimensions considered by the JCVI and NICE were analysed and mapped against the selected vaccines and their broader value elements. Each step was validated by carrying out expert interviews with different stakeholders. We provided recommendations that address the gap between the potential broader value of future vaccines and the value elements recognized by key regulators in the UK today.

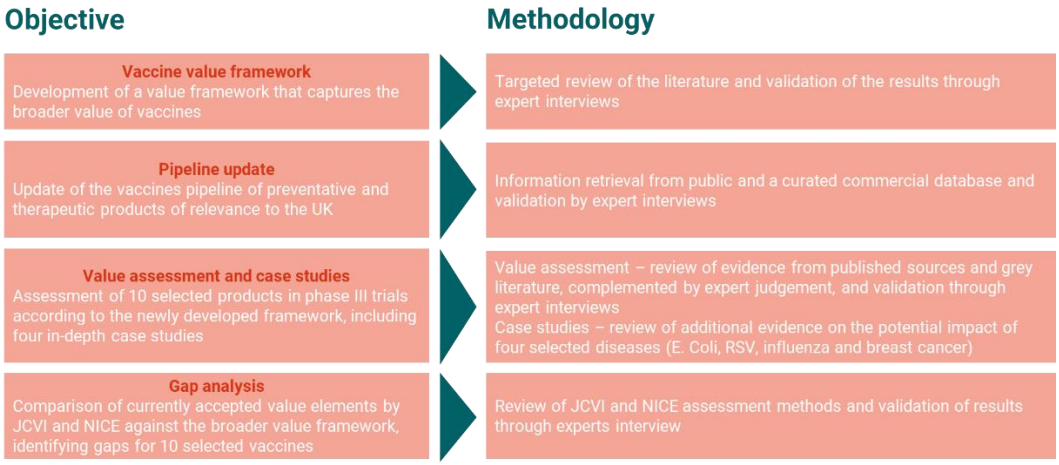

Figure 1: Methodology overview

2.1 Value framework for vaccines

We conducted a targeted review of the literature discussing methods and value frameworks for assessing the full value of vaccines. Our review focussed on peer-reviewed publications known to the authors and relevant references from those papers. A search was also conducted in Google and Google Scholar using the terms: 'vaccines economic value', 'vaccines economic assessment', 'vaccines health technology assessment', 'vaccines HTA criteria' to ensure that we did not miss any key papers.

This literature review informed the development of a comprehensive framework that captures the impact of vaccines from a societal perspective. Given the geographical scope of this project, we focussed on the dimensions of value that are expected to be relevant in the context of high-income countries.

The proposed value framework and its components were tested in a round of interviews with five members of the ABPI Vaccines Group and three experts with knowledge of vaccines assessment

approaches and vaccination policies in the UK and globally. The framework was then revised according to the feedback received and used in the value assessment exercise.

2.2 Pipeline Update

Data retrieval was carried out for preventative and therapeutic vaccines, using publicly available information between July and August 2019. The overall retrieval process is visualised in Figure 2. First, we merged the contents from the WHO Vaccines pipeline tracker and the vaccines pipeline published by the Pharmaceutical Research and Manufacturers of America (PhRMA) (2017). Second, we complemented this dataset with eight individual company[1] pipelines that are either large contributors to the global vaccine supply (Access to medicine foundation, 2017) or members of the ABPI Vaccines Group. Finally, we used the commercial product pipeline database 'Pharmaprojects' (Pharma Intelligence, 2019) to complete and validate the publicly available information.

Vaccines in Pharmaprojects were identified using the following therapeutic classes: prophylactic vaccine, anti-infective; therapeutic vaccine, anti-infective; anticancer, vaccine; recombinant vaccine. The list generated by Pharmaprojects was compared with product names, vaccine type and sponsor company from the list created by steps 1 and 2 mentioned above. Clear instances of duplicates were excluded. Where there were instances of similar but not identical names, or where vaccines were reported in different phases, additional sources, notably company websites and clinicaltrials.gov, were used to confirm whether these were duplicates.

Vaccines were excluded from the dataset if they were of no relevance to the analysis. Criteria for exclusion included vaccines targeting a disease that the National Health Services (NHS) considers as having minor relevance for the UK[2], vaccines that did not fall within phase I – III trials or vaccines for which the development status retrieved from Pharmaprojects revealed that they were either already marketed or withdrawn. Duplicates where removed based on the product name, sponsor and phase.

[1] Respective companies were: Daiichi Sankyo (2019) , GSK (2019) , Pfizer (2019), Sanofi (2019), Johnson & Johnson (2019), MSD (2019), Sequirus (2019) and Takeda (2019).
[2] These diseases were: Denque Fever, Ebola, Lassa Fever, Nipah Virus, MERS, Malaria, Zika, West Nile Virus, Plaque / Yersinia Infections. We are aware, however that these may have an impact on the health of UK's population through an endemic risk but this was considered out of scope for this project.

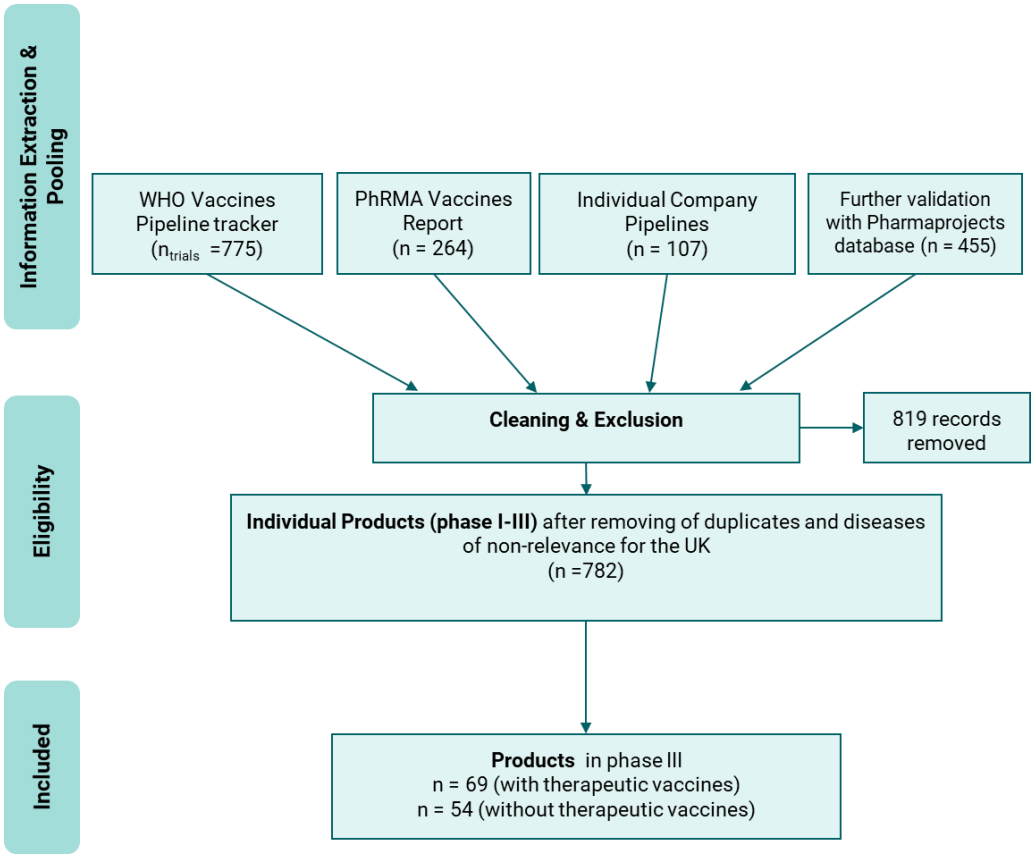

Figure 2: Flow chart of data retrieval

To differentiate the final list of vaccines further, we extracted additional information for each of the vaccines in phase III. Here, we used data from clinical trial databases (such as clinicaltrials.gov), publicly available company information and information from the commercial Pharmaprojects database. Basic information on each vaccine included its manufacturer/licensee, indication (including targeted disease and eligible population) and the corresponding ICD 11 chapter classification of the underlying disease. Furthermore, we retrieved, where available, information to estimate the expected launch date in the UK, to specify the corresponding vaccine type and assess if the vaccines used a preventative or therapeutic approach:

- Where possible, the expected launch date was estimated by adding an average of 1.2 years to the expected phase III trial completion date to account for the approval processes (Kaitin and DiMasi, 2011). If the expected trial completion date was not available, the average duration of 3.3 years from the start of a phase III trial to the expected market launch was added based on (Mestre-Ferrandiz, Sussex and Towse, 2012).

- We used the vaccine type provided by the U.S. Department of Health & Human Services (2017). Hence vaccines fall either into the category of *live-attenuated vaccines*, *inactivated vaccines*, *subunit, recombinant, polysaccharide and conjugate vaccines* or *toxoid vaccines*. In addition, the categories *DNA Vaccines*, *Virus-like particles* were added to capture newer developments as well as immuno-oncology therapy in the case of therapeutic cancer vaccines.

- Therapeutic vaccines were classified by checking the product name, indication or – where available – information from clinicaltrials.gov for the keyword "prevention" and "preventative".

Furthermore, we assumed that every vaccine targeting neoplasms was a therapeutic vaccine. In any other case of doubt, the vaccine was classified as preventative.

In further analysis, preventative and therapeutic vaccines in the pipeline were considered separately. The analytic process was validated by five experts from the vaccines industry with experience in market access and value assessment in the vaccines field in the UK.

2.3 Value assessment

The objective of the value assessment was to identify the dimensions of the framework where future vaccines are expected to deliver the greatest value. We conducted this exercise on a reduced sample of vaccines (n=10) in Phase III development that was considered to be broadly representative of 1) the disease areas targeted by the global pipeline of preventative and therapeutic vaccines, 2) different disease types (e.g. seasonal, infectious diseases), and 3) target population age or other population subgroups. The vaccines in Phase III development were screened according to these criteria and the final sample for the value assessment was decided upon by an in-depth discussion with the ABPI Vaccines Group. Using information from the pipeline differentiation, sources in the published and grey literature, or expert judgement when available evidence was limited, we then identified the dimensions of the framework where the selected vaccines could potentially generate added value. This was assessed by considering the current standard of care for treating/ preventing the targeted disease and the vaccine indication (i.e. population tested in clinical trials). The reasoning behind our assessment of the selected vaccines in the context of the new value framework was discussed and validated through eight interviews: five interviewees had an industry background, two interviewees were experts in international and national market access and value assessment related to vaccines and one interviewee was a representative from the JCVI.

Finally, we developed four case studies on Escherichia Coli infection, respiratory syncytial virus (RSV) infection, influenza and breast cancer. This selection was on a deliberative process with the ABPI Vaccines Group to select a balanced set of vaccines with different profiles and a variety of relevant value elements, not necessarily the four vaccines with the most promising value profiles in the pipeline. In the case studies, we reviewed and documented examples of the current health and economic impact of these diseases, thus providing supporting examples of the potential added value of preventative and therapeutic vaccines.

2.4 Gap analysis

With the 'gap analysis,' we put the results of the value assessment in the context of the UK vaccines appraisal methods. By comparing the results of the value assessment with the methods currently adopted by JCVI and NICE to assess preventative and therapeutic vaccines, respectively, the 'gap analysis' identifies whether the broader value of vaccines is recognised or not.

We reviewed JCVI published documents that discuss the methods used to assess preventative vaccines (DHSC, 2018a, 2019; JOINT COMMITTEE ON VACCINATION AND IMMUNISATION, 2013) to understand whether the dimensions of our value framework are currently part of the appraisal methods of preventative vaccines. The results of this review were validated in an interview with a representative of the JCVI. We also reviewed the NICE guide to the methods of technology appraisal (NICE, 2013) and a systematic review of HTA in Europe by Angelis et al. (2017) to identify the value dimensions that are taken into account by NICE when assessing drugs and therapeutic vaccines.

This can inform further discussions on how to improve the recognition of the broader value of future vaccines and the areas that should be prioritised as part of this discussion.

3 Results

3.1 Value framework for vaccines

As in the case of pharmaceuticals, economic evaluations are used by health systems decision-makers to determine the cost-effectiveness of vaccines and inform the allocation of scarce resources under limited budgets. The methods used to assess vaccines mimic those established by NICE. Irrespectively of the health-related intervention, currently, these methods do not capture the 'broader' effects which are valuable to decision-makers within the healthcare system, as well as to the broader society (e.g. the Treasury). However, the exclusion of value elements such as productivity value or value to carers limits the total value of vaccination programmes more than that of other health-related interventions. This is especially driven by the positive externalities that many vaccination programmes generate, in addition to health-related benefits to the individuals treated. Indeed, traditional approaches focus on the short-term effects that accrue to the vaccinated individuals but typically fail to capture long-term outcomes and wider externalities (Deogaonkar et al., 2012). Bärnighausen et al. (2011), for example, conducted a systematic review of studies evaluating the cost-effectiveness of vaccines for haemophilus influenzae type b and found that the benefits included in the evaluation of the short-term impact on the vaccinated individuals and their direct carers, such as patient health gains, health-care-associated costs, and days of work missed by a carer to look after a patient.

If the full benefits of vaccination are not adequately captured, the cost-effectiveness of vaccines will be systematically underestimated, potentially resulting in suboptimal allocation of resources. The inclusion of broader value elements that allow capturing the full benefit of vaccines is warranted, as long as the same methods are used for assessing non-vaccines interventions that are reimbursed from the same budget (Jit and Hutubessy, 2016; Beutels, Scuffham and MacIntyre, 2008).

Below we set out a value framework which aims to capture both 'narrow' and 'broader' value dimension of vaccines. The framework builds on previously published vaccines frameworks (Bärnighausen et al., 2011, 2013; Deogaonkar et al., 2012; Jit et al., 2015b), with a focus on the dimensions of value that are expected to deliver greater impact in the context of high-income countries.

Our framework distinguishes four value categories: (1) health effects, (2) productivity-related impact, concerning the impact of vaccines on vaccinated individuals and their informal caregivers, (3) community/ health system externalities, namely the health impact of vaccines on the unvaccinated population, and (4) health system economic impact.

1. Health effects

- **Impact on patients QoL.** Impact on patients' physical, mental, emotional, and social functioning. Ideally, the overall QoL assessment should also capture the so-called 'peace of mind' or 'utility in anticipation' benefits, occurring when the quality of life of vaccinated individuals and their carers improves from a reduction in anxiety of severe illness and associated disruptions to normal daily life (Beutels, Scuffham and MacIntyre, 2008; Ultsch et al., 2016).

- **Impact on caregivers QoL.** Impact on caregivers' physical, mental, emotional, and social functioning. As noted above, 'peace of mind' and 'utility in anticipation' benefits will also be relevant to caregivers of children (Beutels, Scuffham and MacIntyre, 2008). This is

particularly true in the case of parents, who will gain utility from the moment of vaccination until the time that the illness was expected to occur knowing that their children are protected against adverse vaccine-preventable outcomes (Drummond, Chevat and Lothgren, 2007).

- **Impact on patients' length of life.** Impact on length of life and mortality.

2. **Productivity related impact**

   - **Impact on patients' productivity.** Impact on work productivity due to sickness or death of the patient. This should capture the impact on lost days of work and on the level of productivity at work, both for getting vaccinated and for disease avoided. Regarding the latter, it has been argued that vaccines can benefit 'outcome-related productivity' by providing protection from diseases that can affect individuals' ability to achieve/ maintain full cognitive potential, higher educational levels, and ultimately work productively during their lifetime (Bärnighausen et al., 2011).

   - **Impact on caregivers' productivity.** Impact on caregivers' work productivity due to caring for a patient.

3. **Community or health system externalities**

   - **Burden of disease in the UK.** The aggregate impact of disease in terms of total disability-adjusted life years (DALYs) or quality adjusted life years (QALYs) lost. Burden of disease may also partly reflect societal preferences for equity. In fact, it has been argued that society places more value on the health gains accrued to worse off population groups, therefore an efficiency-equity trade-off may improve the allocation of resources (Nord, 1999).

   - **Transmission value.** Impact on disease transmission patterns and associated morbidity. Vaccines for infectious diseases can have an impact on population-wide epidemiological outcomes by providing herd immunity to unvaccinated individuals (Bärnighausen et al., 2011; Jit and Hutubessy, 2016). Herd immunity effects can be included in economic evaluations using dynamic modelling approaches (Choi et al., 2011; Christensen et al., 2014).

   - **Prevention of antimicrobial resistance (AMR) development and transmission.** Impact on the rate of development and transmission of resistant infections. Vaccines targeting resistant bacterial infections can reduce the transmission and growth of AMR. Vaccination also the obviates the need to prescribe antibiotics, thus slowing down the development of antimicrobial resistance individuals (Bärnighausen et al., 2011; Jit and Hutubessy, 2016). Overall, vaccine impact on AMR can be considered as another population-wide epidemiological benefit.

   - **Enablement value**. Impact on the cost-effectiveness of other non-vaccine interventions. It has been argued that vaccines should not be evaluated in isolation because they enhance the effectiveness of other non-vaccine interventions (Jit and Hutubessy, 2016). For example, a vaccine for patients with HIV may enable cancer treatment with chemotherapy, which is otherwise a non-recommended option in people with already weak immune systems. A similar value element has been proposed in a value framework for antibiotics by Karlsberg Schaffer et al. (2017), where it is argued that antibiotics can help to prevent and treat serious infections that may be acquired following surgical procedures.

4. **Health system economic impact**

   - **Cost off-sets to the health system**. Impact on medical costs borne by the health system from potential reductions in the number of GP and specialist consultations, treatment, screening interventions and hospitalisations. Ideally, a full assessment of the cost-offsets to the health system will also include the impact on spending on prevention and control activities of infection outbreaks (Jit and Hutubessy, 2016). Compared to most of the other health-related interventions, vaccines might further reduce the pressure on health care systems as the long-term 'peace of mind' that follows the initial vaccination may lower the rates of unnecessary clinical visits (Bärnighausen et al., 2013).

The literature on the broader value of vaccines has also argued in favour of a link between vaccines and economic development. For example, vaccines can generate 'behaviour-related gains' from improving child health and survival patterns, which in turn affect household fertility, consumption choices and maternal labour participation (Bärnighausen et al., 2011). Vaccines can also impact macroeconomic growth as a result of long-term changes to labour supply and foreign direct investments (Deogaonkar et al., 2012). However, our value framework does not include these benefits because these are arguably more important in the context of middle-/low-income countries.

3.2 Pipeline Update

The updated pipeline summary of vaccines of relevance to the UK resulted in 782 products currently in phase I, II or III. Of those, 478 (61%) were classified as preventative vaccines and 304 (39%) were classified as therapeutic.

For both vaccine types, development activity is heavily concentrated: almost 90% of all preventative vaccines in development target infectious or parasitic diseases[3] while 85% of all therapeutic products in development target neoplasms (see Figure 3).

[3] *NB: The ICD 11 class "Infectious or parasitic diseases" captures all diseases that spreads from one humane to another. Hence many of vaccine-preventable diseases are part of this class, reaching from HIV, HPV, Influenza*

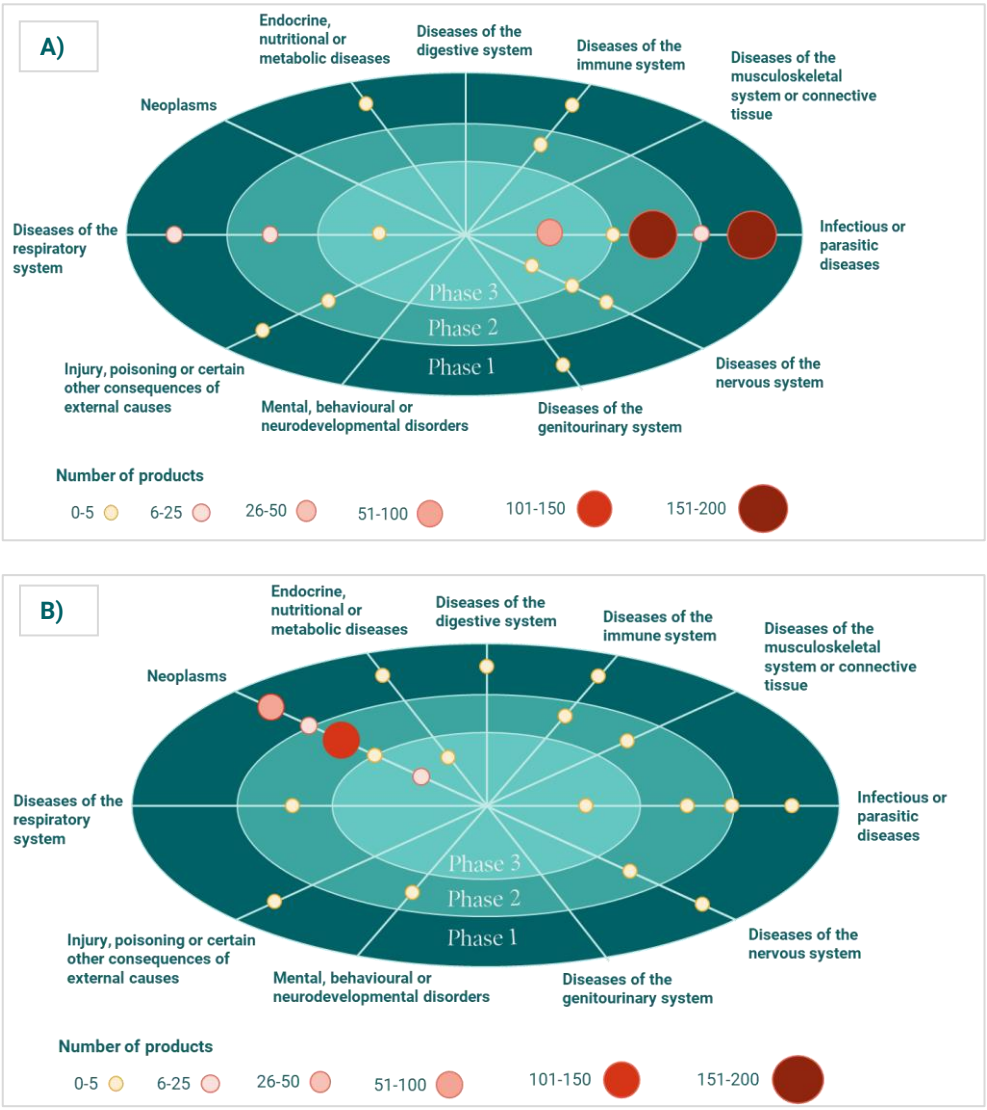

Figure 3: Results of the pipeline update: Preventative (Panel A) and Therapeutic (Panel B) vaccines between phase I and phase III

Among preventative vaccines, there is a relatively high development activity for products targeting influenza, pneumococcal disease and products combining vaccination against five diseases (diphteria, haemophilius, pertussis, polio and tetanus) with a total of 28 active developments (52% of total preventative phase III developments). Activity within the other ICD 11 classes is more evenly spread with mostly one or two developments per class except for products targeting Pneumococcal Disease and Tuberculosis (see Figure 4, Panel A).

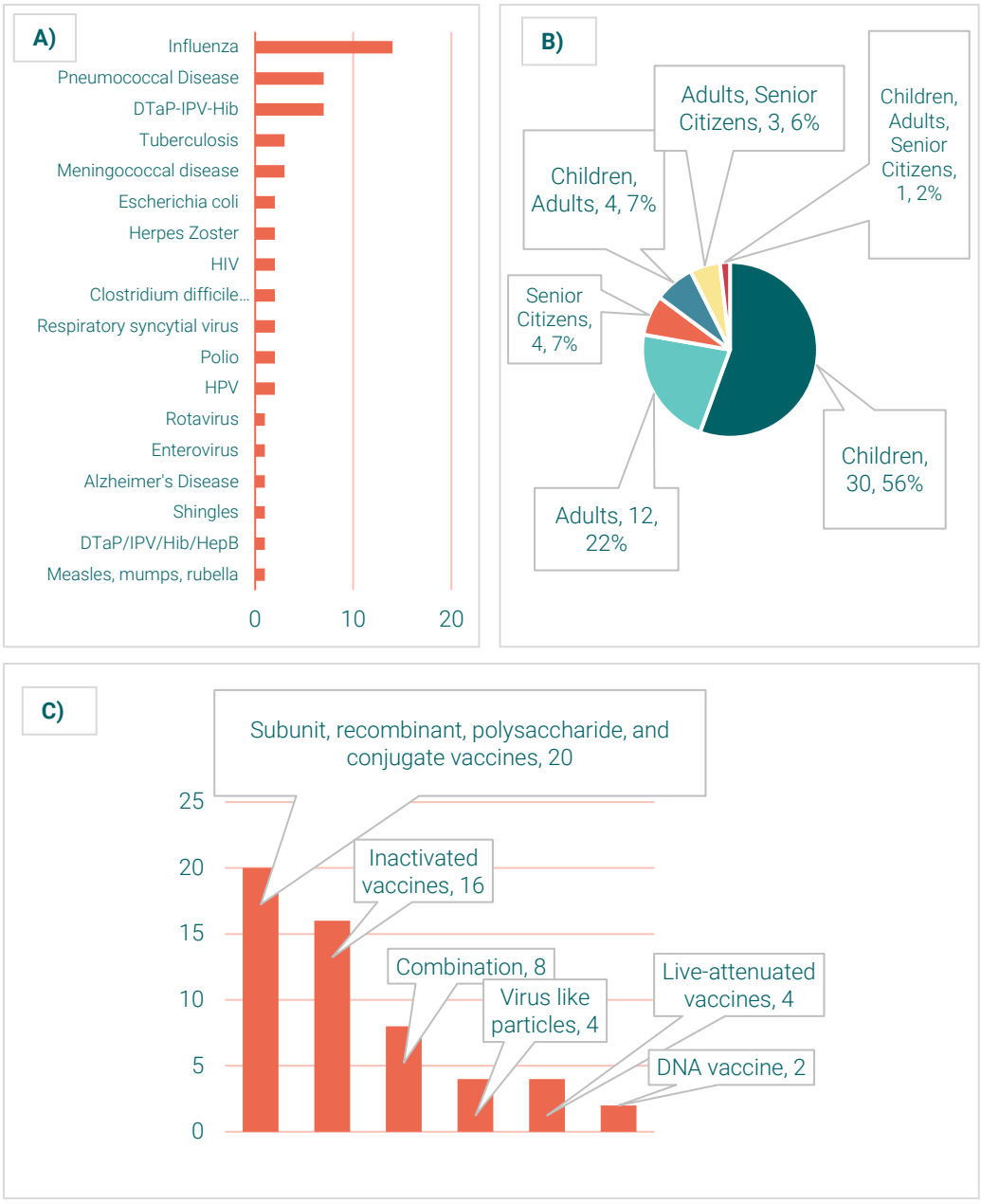

Figure 4: Descriptive Statistics. Preventative products in phase III by: targeted disease (Panel A), target population (Panel B), vaccine type (Panel C).

More than 50% (n=30) of preventative vaccines of the phase III vaccines in the pipeline target children, 22% (n=12) target adults and 7% (n=4%) senior citizens. Around 13% (n=7) of vaccines are targeting a mix of those populations (see Figure 4, Panel B). Most vaccines in phase III are either subunit, recombinant, polysaccharide, or conjugate vaccines that use specific pieces of the germ (i.e. its protein), or are inactivated vaccines that make use of the killed germ that caused the disease (see Figure 4, Panel C). There are only two preventative DNA vaccines in phase III of the pipeline and both target HIV.

As can be seen in Figure 5, most (67%) of the therapeutic vaccines in phase III target different types of cancer (Panel A) and focus generally on an adult population (Panel B). Hence, immuno-oncology products are the leading type of therapeutic vaccines (Panel C).

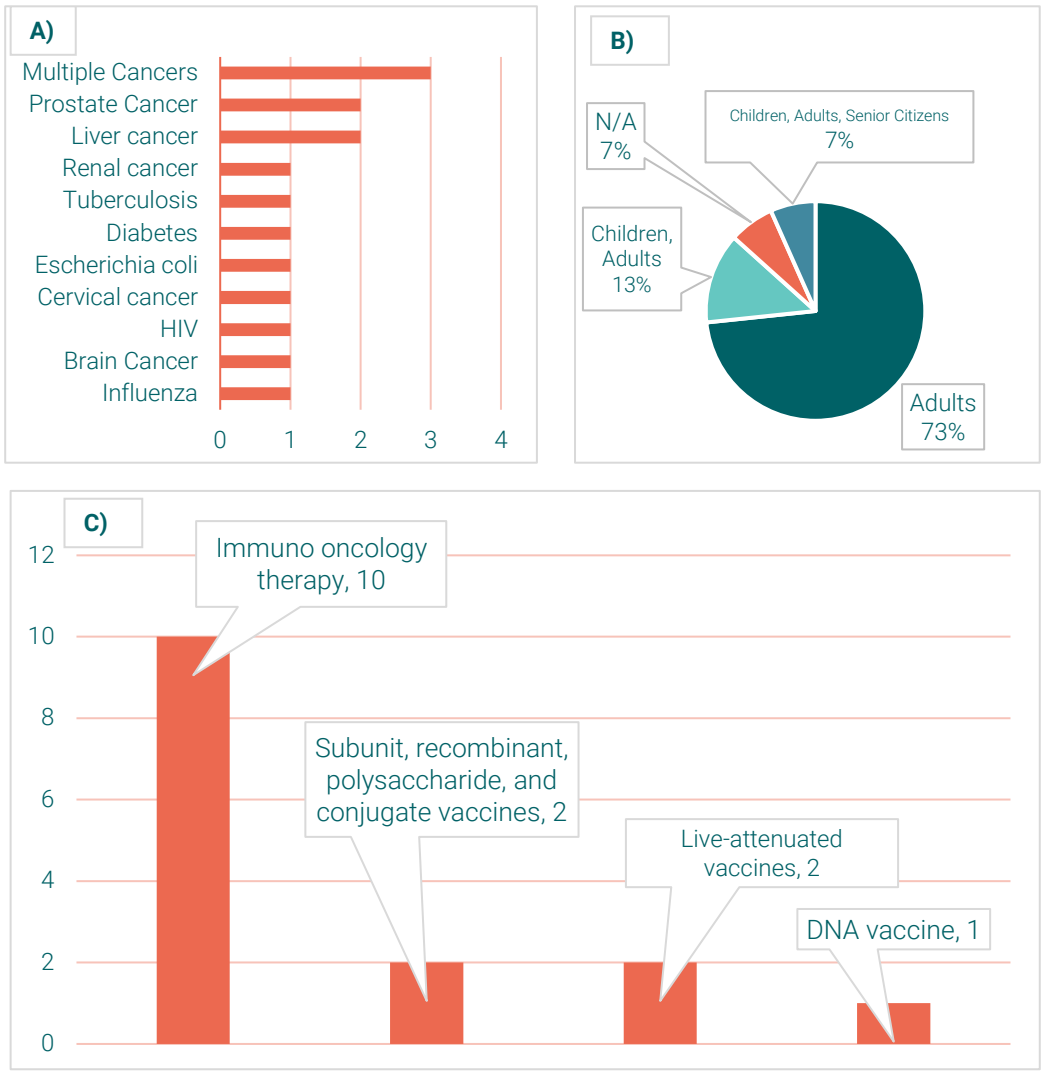

Figure 5: Descriptive Statistics. Therapeutic products in phase III by: targeted disease (Panel A), target population (Panel B), vaccine type (Panel C).

3.3 Value assessment

Table 1 visualises the results from an assessment of 10 selected vaccines currently in phase III against the new value framework. The value dimensions were assessed using a binary scoring (i.e. relevant, non-relevant). We refer the reader to Appendix A for a detailed description of the methodology used to assign the 'burden of disease' scores. A longer version of the table detailing the intuition behind the assessment score is also provided in table B1 and B2 of Appendix B.

In the case of the respiratory syncytial virus vaccination programme, for example, all value elements, except the impact of QoL of carers and the impact on productivity, are 'potentially relevant'. In other

words, the future vaccination programmes are likely to produce significant value for those value elements coded in light green, while this is unlikely for those value elements that are coded in red. In addition, RSV is a main contributor to the total disease burden in the UK as it is part of the 20% of diseases that account for 80% of the total disease burden in the UK, as the value element 'Burden of disease in the UK' is coded in dark green.

Table 1: Value assessment summary table

DISEASE	POPULATION VACCINE TYPE	VALUE ELEMENTS									
		Impact on the QoL of patients	Impact on QoL of carers	Impact on length of life	Impact on patient productivity	Impact on carer productivity	Burden of disease in the UK	Enablement Value	Transmission value	Prevent AMR development	Cost-offsets to healthcare system
HIV	Adults Preventative										
Influenza	Children, Adults Preventative										
Alzheimer	Adults Preventative										
Respiratory syncytial virus (RSV) infection	Adults, Senior Preventative										
Escherichia coli infection	Adults Preventative										
Meningococcal infection	Children Preventative										
Varicella zoster virus infection	Children Preventative										
Diabetes, Type 2	Senior Therapeutic										
Breast cancer	Adults Therapeutic										
Prostate cancer	Adults Therapeutic										

Colour coding: Potentially relevant; Potentially non-relevant; Top 20% contributor to total burden of disease

3.4 Case studies

In addition to the assessment of the 10 selected vaccines, a subgroup of three preventative and one therapeutic vaccine was assessed in 4 case studies.

3.4.1 Escherichia Coli – preventative, adults

DISEASE	POPULATION VACCINE TYPE	VALUE ELEMENTS									
		Impact on the QoL of patients	Impact on QoL of carers	Impact on length of life	Impact on patient productivity	Impact on carer productivity	Burden of disease in the UK	Enablement Value	Transmission value	Prevent AMR development	Cost-offsets to healthcare system
Escherichia coli infection	Adults Preventative										

Escherichia Coli (E. Coli) is a bacterium that is commonly found in the human digestive system and warm-blooded animals. While most E. Coli strains are harmless, certain strains can cause severe foodborne diseases (WHO, 2018a), urinary tract infection, cystitis (infection of the bladder), and intestinal infection. E. coli bacteraemia (bloodstream infection) may be caused by primary infections spreading to the blood. Most people recover from the infection within a week, but more severe cases may become life-threatening. Risk of serious illness and death from E. Coli is higher among the elderly, young children and immunocompromised individuals (WHO, 2018a). E. Coli infections with hospital-onset are usually characterised by higher case fatality rates than infections with community-onset, given the typically worse comorbidities of the hospital patient population (Bhattacharya et al., 2018).

Health effects

E. Coli infections can affect patients' long-term QoL. In particular, patients' mental health may be worse than the general population's for six months (Löwe et al., 2014) to one year (Riegel et al., 2015) after recovering from the infection. E. Coli infections may also be responsible for the development of chronic conditions, such as chronic fatigue (Riegel et al., 2015).

Community or health system externalities

E. Coli is generally transmitted through consumption of contaminated foods (WHO, 2018a). However, in recent years the number of hospital-associated E. Coli infections has increased. In England for example, the incidence of E. Coli bacteraemia has increased, and about 60% of these cases have had a hospital-onset or have manifested in hospital-discharged patients with a history of healthcare interventions, such as urinary catheterization or antibiotic therapy within the previous four weeks (Bhattacharya et al., 2018; Health Foundation, 2017).

E. Coli is one of the multiple causes of diarrhoeal disease and urinary tract infections, which are responsible for 0.29% and 0.36% of the total DALYs lost in the UK due to disease respectively. The bacterium is also responsible for 84% of the total burden of bloodstream antibiotic-resistant infections in England (Public Health England, 2018). Between 2014 and 2018 the incidence of these infections due to E. Coli has increased by 12%. Resistant E. Coli infections for which antibiotics do not work may prevent surgeries in patients with compromised immune systems.

Health system economic impact

E. Coli infections result in physician visits, emergency department visits and hospitalisation. The value of medical care associated with E. Coli infections has been estimated to represent about 14% of the total economic cost of this infection (Frenzen et al., 2005). A study by Naylor et al. (2017) using data from the English national surveillance database estimated that E. Coli infections increase hospital length of stay by about 4 days relative to non-infections (Naylor et al., 2017), while in the case of resistant infections the excess hospital length of stay compared to susceptible infections is 1.58 days. The same study estimated that the overall hospital costs to E. Coli bacteraemia in England is in the range of £14 million per year.

Productivity related impact

A study of the economic cost of E. Coli estimated that the number of days missed from work ranges from 0.25 days, for patients that do not see a physician, to 7.13 days, for hospitalised patients (Frenzen et al., 2005). The value associated with this loss in productivity represents 1.2% of the total economic cost of E Coli.

3.4.2 Respiratory Syncytial Virus (RSV) – preventative, adults/elderly

DISEASE	POPULATION VACCINE TYPE	VALUE ELEMENTS									
		Impact on the QoL of patients	Impact on QoL of carers	Impact on length of life	Impact on patient productivity	Impact on carer productivity	Burden of disease in the UK	Enablement Value	Transmission value	Prevent AMR development	Cost-offsets to healthcare system
Respiratory syncytial virus (RSV) infection	Adults, Senior Preventative										

Respiratory syncytial virus (RSV) infections are a leading cause for acute bronchiolitis, upper and lower respiratory tract infections. These infections are collectively responsible for 2.11% of the DALYs lost in the UK due to disease (IHME, 2017). The incidence of RSV is higher among patients with comorbidities, who are also at higher risk of developing complications such as apnoea and acute otitis media. Higher risk groups include pre-term infants, patients with immunological disorders, frail elderly, patients with cardiorespiratory disease. RSV is a seasonal disease, with higher incidence and transmission rates in the winter months. The virus can spread through contact/ proximity with an infected person or place (CDC, 2018b).

Health effects

There is growing evidence that RSV lower respiratory tract infections in early childhood are associated with long-term respiratory morbidity, wheezing and asthma later in life, resulting in reduced quality of life and increased healthcare resource use (Fauroux et al., 2017). In the adults and the elderly, exacerbations of RSV infections can be responsible for the faster physical decline and longer recovery time compared to exacerbations of bacterial infections (Díez-Domingo et al., 2014).

In developed countries, the childhood mortality risk associated with RSV infections is almost negligible, but only among those without severe complications. In adults and the elderly, mortality rates mirror those of influenza, ranging between 4% and 8%, but are significantly higher among hospitalised patients (Díez-Domingo et al., 2014). Particularly in elderly or hospitalised patients, with relatively fragile health, severe RSV infections may hinder or prevent the treatment of other diseases.

Productivity related impact

RSV has been found to affect the productivity of parents up to one month after discharge, in the case of hospitalised patients in the child age. Specifically, parents miss from an average of 23-24 days of work at discharge to an average of 2-4 hours of work one month after discharge (Pokrzywinski et al., 2019). At present, there is no available evidence of productivity losses of caregivers attending elderly patients.

Health system economic impact

Elderly patients affected by RSV show higher rates of utilisation of healthcare resources than children and adults patients (Amand et al., 2018). The greatest source of healthcare resource use from RSV is from outpatient visits. Even though RSV has a viral aetiology, and the rates of bacterial infections complicating RSV are rare (0.6%-1.2% in hospitalised children), antibiotics have been found to be highly prescribed in cases of viral RSV bronchiolitis (Quintos-Alagheband et al., 2017; Amand et al., 2018).

3.4.3 Breast Cancer – therapeutic, adults

DISEASE	POPULATION VACCINE TYPE	VALUE ELEMENTS									
		Impact on the QoL of patients	Impact on QoL of carers	Impact on length of life	Impact on patient productivity	Impact on carer productivity	Burden of disease in the UK	Enablement Value	Transmission value	Prevent AMR development	Cost-offsets to healthcare system
Breast cancer	Adult Therapeutic										

Breast cancer develops in the breast tissue and has a heterogeneous clinical and morphological presentation. Examples of risk factors for breast cancer include being female, obesity, lack of physical exercise, drinking alcohol and personal or family history of cancer (Cancer Research UK, 2017a). Breast cancer is the most common cancer in the UK, accounting for 15% of all new cancer cases in 2016. It also ranks third among the disease responsible for the largest number of years of life lost in women and among the top-10 diseases for number of DALYs lost in women (Steel et al., 2018).

Health effects

Breast cancer affects the quality of life of patients in both the short- and long-term. At diagnosis, patients may suffer mental distress, and during chemotherapy, they may experience fatigue and pain (Paraskevi, 2012a). In the post-treatment stages, patients' mental health may be affected by fear of recurrence, while physical QoL will generally be similar to the general population level, except for potential lymphedema and/or feeling of numbness to the arm (Paraskevi, 2012a). Breast cancer caregivers' may also be affected by mental distress and depression, conditions which are in turn correlated with worse levels of overall QoL (Gorji et al., 2012).

Breast cancer survival rates usually depend on the disease stage at diagnosis, the type of cancer and grade of cancer cells. Five-year survival rates, for example, vary to a significant degree: from 99% for diagnosis at stage one to 15% for diagnosis at stage four (Cancer Research UK, 2017b). Overall, mortality from breast cancer has decreased in a number of high-income countries since the 1990s, thanks to a combination of improved treatment techniques and earlier diagnosis (Stewart and Wild,

2019). Treatment for breast cancer, although highly variable in nature depending on the stage and type of cancer, can prevent or interfere with other treatments, particularly in severely immunosuppressed patients.

Productivity related impact

The work productivity of both patients and informal caregivers are affected by breast cancer. Women with breast cancer or undergoing treatment report substantial impact on both absenteeism and presenteeism (Frederix et al., 2013). Men whose partners are affected by breast cancer are also significantly more likely to stop working during treatment (Bradley and Dahman, 2013). Productivity losses appear to dissipate for informal caregivers in the long term (Bradley and Dahman, 2013), but they can persist for survivors, even three years after treatment (Lavigne et al., 2008).

Health system economic impact

A cross-country review found that the medical costs of breast cancer increase with the disease stage at diagnosis (Sun et al., 2018). In fact, patients with more advanced staged of breast cancer receive more treatments than early-stage patients. On average, estimates of the medical costs of breast cancer at stage two, three and four are 32%, 95%, and 109% higher than costs at stage one respectively.

3.4.4 Influenza – preventative, children/adults

DISEASE	POPULATION VACCINE TYPE	VALUE ELEMENTS									
		Impact on the QoL of patients	Impact on QoL of carers	Impact on length of life	Impact on patient productivity	Impact on carer productivity	Burden of disease in the UK	Enablement Value	Transmission value	Prevent AMR development	Cost-offsets to healthcare system
Influenza	Children, Adults Preventative										

Influenza is a viral infection which manifests with sudden onset of fever, cough, headache, muscle and joint pain, sore throat and runny nose. During the illness episode, influenza has been found to affect all domains of health-related QoL, as measured by the EQ-5D dimensions of 'mobility', 'self-care', 'usual activity', 'pain/discomfort', and 'anxiety/depression'. In particular, 'usual activities' and 'pain' tend to be the most affected domains (Fragaszy et al., 2018a). Symptoms can be debilitating, but most people are able to recover within a week of feeling ill. However, influenza can cause severe illness or death in people at higher risk. In developed countries, population groups at higher risk of complications are people aged 65 or older (WHO, 2018b).

Health effects

Seasonal influenza is transmitted easily, through contact/ proximity with infected people. Among the population groups at higher risk of contracting influenza are pregnant women, children under 59 months, the elderly, individuals with chronic medical conditions and with immunosuppressive conditions (WHO, 2018b). In temperate climates, seasonal influenza epidemics occur mainly during the winter, while in tropical regions, influenza may occur throughout the year, causing outbreaks more irregularly (WHO, 2018b).

Productivity related impact

People affected by influenza may experience short-term productivity losses due to the debilitating symptoms and the infectious nature of the disease, which may require withdrawal from the workplace (Franklin and Hochlaf, 2018). An analysis of data from the Flu Watch cohort study in England estimated that children affected by influenza A and B miss on average 2.1 and 3.5 days of school in 31% and 56% of the cases, respectively (Fragaszy et al., 2018a). The same study found that children are more likely than adults to require someone else to take care of them, with implications for the short-term productivity of caregivers. In fact, in about half of the cases, adults in working-age took on average between 3.4 and 5 days off work to take care of their children. Most patients fully recover from influenza, with negligible effect on long-term personal and caregivers' productivity.

Community or health system externalities

The clinical burden of individual episodes of influenza is low, but the total burden of influenza at the population level is large. The Burden of Communicable Diseases in Europe study 2009-2013 (Cassini et al., 2016) estimated that, among a selected group of infectious diseases surveyed by the European Centre for Disease Control, influenza is responsible for 29.8% of the total number of DALYs lost. Overall, influenza has a high burden in all population age groups. These results appear to be driven by high incidence rates of influenza.

Health system economic impact

The economic burden of influenza to the health system is driven by the cost of the associated inpatient and outpatient services. A systematic review of the medical costs of influenza found that, on average, inpatient and outpatient services account for 43.5% and 44.5% of the total cost per episode of influenza, respectively (Federici et al., 2018). Hospitalisation events are expensive but rare, while outpatient medical services are less expensive but more frequent.

Despite its viral aetiology, episodes of influenza are associated with the inappropriate prescription of antibiotics. Analysis of cohort data from the 2013-14 and 2014-15 influenza seasons in the US has shown that antibiotics were prescribed in approximately 30% of the cases of influenza with no diagnosis of pneumonia (for which antibiotic prescription is indicated) (Havers et al., 2018).

3.5 Gap analysis

Table 2 shows whether the value elements of our value framework are likely to be considered in vaccines appraisals by the JCVI or NICE. Note however there may be instances where the guidelines do not formally state the inclusion of a value element but, in practice, special allowances may be made deliberatively on a case-by-case basis.

Table 2: Value elements considered by the JCVI and NICE

	VALUE ELEMENTS									
	Impact on the QoL of patients	Impact on QoL of carers	Impact on length of life	Productivity of patients	Productivity of carers	Burden of disease in the UK	Enablement value	Transmission value	Prevent AMR development	Cost-offsets to healthcare system
JCVI's ASSESSMENT CRITERION?	▲	▲	▲	✖	✖	▲	✖ [4]	▲	✖ [1]	▲
NICE's ASSESSMENT CRITERION?	▲	▲ [2]	▲	✖	✖	▲ [3]	✖ [4]	✖ [6]	✖ [5]	▲

▲ Likely to be considered by JCVI/NICE ✖ Not likely to be considered by JCVI/NICE

Notes: [1]The JCVI advises further research in quantifying the potential impact of vaccines in reducing the long-term burden of AMR (https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation#research-recommendations); [2] Carers' impact on QoL is considered when relevant: "The perspective on outcomes [includes] all direct health effects, whether for patients or, when relevant, carers"; [3]Burden of disease is considered deliberatively. Severity is considered by means of the 'end of life' criteria, which allow a different weighting of the cost-effectiveness threshold when specific conditions are met; [4] The JCVI can in principle consider Enablement value. However, this is often not possible due to a lack of data or because the impact of this element is expected to be small. In such cases the enablement value may be part of the deliberative process (but not captured in the actual modelling); [5] The DHSC has announced a pilot programme of a 'volume-delinked' payment scheme, which will include a modified assessment approach of antibiotics. [6] It should be noted that NICE has no experience so far of assessing vaccination programmes and that normal health-related interventions do not create much transmission value. Consideration of transmission value by NICE may be likely if the assessment of vaccination programmes is included in their remit.

Table 3, combines the results of the value assessment exercise (Table 1) and the analysis of the JCVI/NICE assessment criteria (Table 2), showing the potential areas of discrepancy between the relevant elements of value of vaccines and those that do not enter the vaccines appraisal (cells green with red cross symbol).

The results of Table 3 should be interpreted with some caveats in mind. For example, the JCVI would be willing to consider the impact of vaccines on preventing AMR if evidence of cost/QALY was available. In recognition of AMR as a public health threat, a recommendation for generating evidence of this impact has been made. Depending on the definition used and the associated measurement unit (preferably in QALY or cost terms), 'enablement' value could also enter the assessment. Alternatively, where it is clear that a significant element of health benefit or cost saving is not included in the ICER, the JCVI will consider the most appropriate way to adjust this estimate (JOINT COMMITTEE ON VACCINATION AND IMMUNISATION, 2013).

Table 3: Gap analysis

DISEASE	POPULATION VACCINE TYPE	VALUE ELEMENTS									
		Impact on the QoL of patients	Impact on QoL of carers	Impact on length of life	Impact on patient productivity	Impact on carer productivity	Burden of disease in the UK	Enablement Value	Transmission value	Prevent AMR development	Cost-offsets to healthcare system
HIV	Adults Preventative	▲	▲	▲	✗	✗	▲	✗	▲	✗	▲
Influenza	Children, Adults Preventative	▲	▲	▲	✗	✗	▲	✗	▲	✗	▲
Alzheimer	Adults Preventative	▲	▲	▲	✗	✗	▲	✗	▲	✗	▲
Respiratory syncytial virus (RSV) infection	Adults, Senior Preventative	▲	▲	▲	✗	✗	▲	✗	▲	✗	▲
Escherichia coli infection	Adults Preventative	▲	▲	▲	✗	✗	▲	✗	▲	✗	▲
Meningococcal infection	Children Preventative	▲	▲	▲	✗	✗	▲	✗	▲	✗	▲
Varicella zoster virus infection	Children Preventative	▲	▲	▲	✗	✗	▲	✗	▲	✗	▲
Diabetes, Type 2	Senior Therapeutic	▲	▲	▲	✗	✗	▲	✗	✗	✗	▲
Breast cancer	Adult Therapeutic	▲	▲	▲	✗	✗	▲	✗	✗	✗	▲
Prostate cancer	Adult Therapeutic	▲	▲	▲	✗	✗	▲	✗	✗	✗	▲

4 Discussion

4.1 Challenges

The current vaccine pipeline shows significant development activity for preventative and therapeutic vaccines. The retrieved data did not always allow for an estimation of the expected launch date. However, within the next 5 years, 23 preventative and seven therapeutic vaccines that are currently in phase III could potentially be launched in the UK.

The value assessment of a selected sample of preventative and therapeutic vaccines, which is broadly representative of the disease areas, patient ages and population groups targeted by the global Phase III development pipeline, demonstrated the broader value that resides within the vaccination pipeline. Specifically, all of the 10 selected vaccines are likely to deliver cost-offsets to the healthcare system[4]. Further, seven are likely to produce gains in patient productivity and eight are likely to produce a gain in carer productivity. A few vaccines enable potential health-related interventions that would not be possible without the vaccination or contribute to tackling the threat of AMR.

The gap analysis revealed that future vaccination programmes may deliver benefits in value dimensions that are currently likely to not be considered in the appraisal of vaccines in the UK. When discussing these results during three interviews with representatives from the JCVI, the BSI and the Wellcome Trust several challenges were identified.

The JCVI currently recognises value elements like the gain in QoL and length of life, burden of disease and cost-offsets to the health care system. Especially important for vaccines is the recognition of transmission value which is important as most vaccines in the pipeline target infectious diseases.

The value dimensions that are currently not likely to enter the cost-effectiveness modelling relate to the productivity gain of patients and careers, the enablement of other health-related interventions through specific vaccination programmes and the reduction in the development of AMR. While for preventative vaccines, the JCVI acknowledges the potential value of suitable vaccination programmes to prevent AMR resistance, including this consideration in the cost-effectiveness quantification requires a better understanding of the patterns of AMR development and models to quantify the impact of relevant vaccination programmes.

If vaccines were to be assessed in the same way as any other public health intervention in the UK, it may be easier to integrate broader value elements as these the methods outlined in the NICE public health guidance (third edition) would generally allow for taking a broader perspective (NICE, 2012).

One challenge, however, is that these value dimensions may not be of equal relevance to different stakeholders. Those with responsibility for health planning, budget development, and management of community-based programmes may be more interested in enablement value and the prevention of AMR. However, senior officers in industrial federations, trade unions or local workers' compensation boards and ministers of finance with broader social objectives (see Mauskopf et al. (2018)), may place greater value in the vast amount of productivity value residing in vaccination programmes. The

[4] Please note that the cost-effectiveness of a vaccine depends a lot on how the programme is delivered. It is of relevance if the vaccine is delivered for the whole population or if it will be possible to reliably identify high-risk groups for administration.

JCVI, however, relies mostly on the NICE methods for cost-effectiveness evaluation and has limited flexibility in making changes that can help recognise broader value dimensions.

One of the major challenges is finding ways to recognise and reward the broader value of vaccination programmes that are realised outside the health system. Productivity gains appear to contribute strongly to the overall value of vaccination: as estimated in another report, the forgone direct and indirect taxes, payments for National Insurance and lost value of informal care is in many cases much larger than the direct medical costs savings due to prevented disease[5]. In order to fully recognise that value, it would require a change of the perspective taken by JCVI (and NICE) to a societal perspective. Such a change would not align with the established NICE reference case (NICE, 2013) and thus would introduce a bias in favour of vaccination programmes, if done for solely for vaccination programmes. Complementary analyses taking a different perspective as outlined in Mauskopf et al. (2018) might represent a valuable alternative for demonstrating and recognising the true value of vaccines.

Finally, if in the future some of the aforementioned broader value elements are to be routinely assessed by decision-makers, reliable evidence and models to quantify that value are required. Here, attention must be paid to capture value accurately. In general, vaccines might generate additional costs in comparison to other health-related interventions, due to stockpiling of products to ensure readiness for potential epidemics.

More specifically, with respect to each value element, factors that may potentially lower their true value may be considered. For example, the productivity loss of the working population from the administration of the vaccine during working hours should be considered. Another example would be that 'peace of mind' benefits or 'utility in anticipation' of patients and their carers might be slightly reduced in the short term due to utility decrements associated with the side effects of vaccination.

Producing the required evidence may be complex and comes at a cost. This will be exacerbated as future vaccines might tackle diseases that affect smaller populations which makes the clinical phase even more lengthy and costly.

4.2 Limitations

This research has some limitations which are linked to the methods applied during the pipeline update and value assessment.

Pipeline update

The vaccine pipeline is dynamic. This results from new vaccines entering phase I trials and phase III trials that may successfully transition to the market approval phase. In addition, during each study phase, each project is at risk of termination due to undesired results in efficacy and safety.

Furthermore, the updated pipeline may exhibit some redundancy. The exact information related to the same vaccine may differ strongly between different databases. Hence, although multiple automatic and manual checks were in place, some duplicate products may not have been detected.

[5] *Please find the detailed methodology in Brassel S. and Steuten L., 2020. The Broader Value of Vaccines – The Return on Investment From a Governmental Perspective. OHE Consulting Report, London: Office of Health Economics. (forthcoming).*

Finally, the mapping of vaccines to ICD 11 classes concentrates the activity in the area of "Infectious diseases" as this captures every disease that spreads, directly or indirectly, from one person to another. This skews the activity in the vaccines pipeline towards infectious diseases.

To deal with these limitations, two main countermeasures were undertaken. Firstly, all vaccines from publicly available databases were complemented with and validated through the curated Pharmaprojects database. Secondly, vaccines from companies represented in the ABPI's Vaccines Group were validated by individual company representatives. Nevertheless, some uncertainty remains.

Value assessment

The value assessment is based on a non-systematic review of published sources discussing the impact of the selected diseases on the dimensions of the value framework. Furthermore, the interview sample was moderately biased towards industry representatives. It is therefore prone to some selection and publication bias. Our objective is, however, to identify areas of potential added value that might be generated by a specific vaccine given the unmet need and current burden of diseases targeted, and hereby progress the discussion on venues for measuring these value dimensions and options for including them in value assessment methods. We did not aim to predict in any way the results of further research on the real-world value of these vaccines.

5 Conclusion

Since the first immunisation by Edward Jenner, vaccination in the UK has come a long way and regulators and governmental bodies have successfully implemented one of the most comprehensive immunisation schedules in the world.

At the same time, a busy vaccines pipeline ensures the future supply of innovative vaccines and the potential eradication of ever more diseases. New developments in preventative vaccines will continue their focus on infectious diseases and provide benefits to unvaccinated people through herd immunity. Therapeutic vaccines, showing strong pipeline activity in the oncology field, are a newer development to deliver on its promise in the (near) future.

There is, however, imminent risk of underestimating the value of future immunisation programmes if the broader value of vaccination cannot be adequately captured. This would be reflected in a potential suboptimal reimbursement and hence may impact the pipeline activity in the long run, as it gets harder for innovators to recapture their return on investment.

This report shows that the future pipeline is likely to provide the UK with vaccines of high value, of which relevant parts are currently not captured completely in the prevailing assessment frameworks. We, therefore, propose a framework to include these broader value elements that, while based on current academic frameworks, focuses specifically on high-income countries like the UK. The complete adoption of our proposed framework would require the adoption of a societal perspective on cost-effectiveness by both NICE and JCVI, which seems unlikely in the short-term. However, the partial recognition of enablement value and the value of vaccines in preventing AMR could be realised in the medium-term by leveraging current modelling and data collection initiatives. In the long-term, new avenues should be explored to recognise and appropriately reward large productivity gains accruing from vaccination programmes, to stimulate ongoing innovation in this important area.

5.1 Recommendations

Based on the results from the gap analysis and the insights gained during the stakeholder interviews, the following recommendations are given in areas where more work is needed in order to pave the way towards the recognition of the broader value of future vaccines. It must be noted that the relevance of these recommendations will depend on the specific vaccination programme, the targeted population, whether the vaccine is preventative or therapeutic and the respective stakeholder group of the addressee.

1. **Recognise the enablement value for non-vaccine interventions and the value in fighting AMR**

   In the case of preventative vaccines, the JCVI is open to considering enablement value as 'added benefits of vaccination'. However, this is strongly dependent on the definition of enablement value, while also ensuring that the outcomes are measured in QALYs. It is therefore recommended to give a clear definition of enablement value and to develop process and methodologies to capture the potential value. A possible solution may be to evaluate vaccines in conjunction with the non-vaccine interventions that will be 'enabled' by the introduction of the new vaccine (Jit and Hutubessy, 2016).

   Vaccines help to reduce AMR by either preventing secondary bacterial infections or by reducing the inappropriate use of antibiotics caused by viral pathogens. To appropriately incentivise the

development of vaccines that contribute to the reduction of AMR, this value should be quantified. A better understanding of the long-term impact of vaccines on the development of AMR and a suitable model that can be applicable to cost-effectiveness analysis should, therefore, be developed.

2. **Find new approaches to recognise the productivity value captured outside the health system's perspective**

   As the JCVI relies on NICE's evaluation methods to assess cost-effectiveness, the perspective of the health system is taken. As such, productivity effects delivered by preventative and therapeutic vaccines that are highly relevant from a broader societal perspective, but not from a health system's perspective, are currently not considered. Recognising this value would require a perspective change for all evaluations of health-related interventions, as otherwise vaccination programmes would be favoured over other interventions competing for the constrained health resources. This perspective change would allow to include broader elements of value but must be combined with a lower decision-making threshold (i.e. incremental costs per QALY gained) because of the constrained healthcare budget. This would in return require to measure the value of vaccines and other health-related interventions according to the new framework and threshold. If vaccines create more value in the broader dimensions (e.g. herd immunity, long-term productivity gains), vaccination programmes would displace other health interventions, other things equal.

   However, NICE (and consequently JCVI) adopts the perspective of the health system in its reference case because a broader one (i.e. societal perspective) may lead to favouring technologies that are less efficient at improving health when non-health benefits are higher than health-benefits. Ultimately, the population outside of the workforce may be disadvantaged by a similar approach.

   Therefore, novel approaches should be explored to capture this value for those who might profit the most from it. Potential avenues might be to promote employer-funded vaccination programmes to different disease areas (other than the current flu vaccination programmes) and potentially family members as this may increase carer productivity. If delivered 'worksite', such programmes would also deal with some of the downsides of administering vaccines (e.g. a reduced productivity loss as less working time is lost due to obtaining the vaccination of the workforce)

3. **Increase transparency and comprehensiveness of value assessment process and stimulate stakeholder engagement**

   The JCVI is transparent in many ways as it publishes meeting minutes, their reasoning with respect to their decision making and, ultimately, information regarding the underlying models. However, discussions from our interviews programme highlighted that innovators would benefit from improved upfront information on recommended methods, stakeholders and clearer online-accessible description of the end-to-end process.

   Most importantly, an earlier and continuous engagement between regulators, innovators and public health specialists using suitable platforms is recommended. This would help to reduce uncertainty for all involved parties and hence increases the efficiency of the market access and appraisal process.

4. **Proactively steer the generation of high quality & relevant evidence**

As for all evaluations of health-related interventions, apart from established and validated methodologies, a robust, high-quality evidence base is a requirement for decision making. In the future, acquiring this evidence may get harder as the clinical indication of future vaccines will get more and more specific and target ever-smaller patient populations. JCVI and NICE should therefore proactively steer the generation of evidence.

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Appendix A 'Burden of disease' measurement approach

To qualify the burden of individual diseases to the UK, we considered the total burden of disease in the UK. For each disease, we obtained data on DALYs lost in the UK from the latest issue of the Global Burden of Disease study (Lancet 2018). The DALY combines the years of life lost (YLL) due to premature mortality and the years of life lost due to disability (YLD) for people living with a specific health condition or its consequences.

First, we sorted the diseases in increasing order by their percentage contribution to the total DALYs lost in the UK. We then applied the 'Pareto principle' as our classification rule to determine whether the burden of disease is particularly relevant to the UK. The Pareto principle establishes that roughly 80% of the effects (in this case the total UK burden in DALYs) stems from the top 20% of the causes (in this case the diseases) (Pareto and Page, 1971). Therefore, it follows that the bottom 80% of diseases are individually responsible for minor burden, because collectively they only account for 20% of the total burden, in DALYs, in the UK.

Based on this we highlighted the diseases appearing in the top 20% of them as 'particularly relevant' in the assessment.

Appendix B Value assessment supporting material

Table B1. Value assessment results (1)

DISEASE	POPULATION	VALUE ELEMENTS 1				
		Impact on QoL of patients	**Impact on QoL of carers**	**Impact on length of life**	**Impact on patient productivity**	**Impact on carer productivity**
HIV	Adults	▪ HIV is nowadays a chronic and manageable disease. HIV may however cause anxiety and depression more than other chronic diseases[1]	▪ HIV caregivers may report poorer psychological health[2]	▪ If untreated, HIV is a deadly condition but with modern treatments, survival rates of people with HIV have improved substantially in the past two decades[3]	▪ Productivity of HIV patients who work is overall similar to that of healthy people[4] ▪ However, HIV is responsible for lower employment rates and premature mortality[4]	▪ Caregiver productivity is likely to decrease in the late stages of the disease when the health of the patient is deteriorating[5]
Influenza	Children, Adults	▪ Influenza symptoms can be debilitating during the illness period, but patients are typically able to regain full health after recovery[6]	▪ Influenza is a curable disease and the episode length is moderate enough to exclude a significant impact on QoL of carers[5]	▪ In developed countries, influenza can cause severe illness or death people aged 65 or older[7]	▪ Productivity losses resulting from missed work days can be frequent but are limited to a few days per episode	▪ Children are likely to require someone else to take care of them, normally adults in working age[8]

DISEASE	POPULATION	VALUE ELEMENTS 1				
		Impact on QoL of patients	**Impact on QoL of carers**	**Impact on length of life**	**Impact on patient productivity**	**Impact on carer productivity**
Alzheimer	Adults	▪ Progressive deterioration of brain functions. In late stages patients become completely dependent on carers[9]	▪ Physical and mental distress of carers increase in the later stages of disease, when patients become completely dependent on carers[10]	▪ Impact on length of life may depending on the age of onset, stage of the disease when diagnosed[9]	▪ Prevalence of disease risk is highest among the retired, non-working population[9]	▪ Early disease stage requires minor carer support, while patients become completely dependent on carers in later disease stages[9]
Respiratory syncytial virus (RSV) infection	Adults, Senior	▪ In healthy individuals, RSV symptoms are mild and typically mimic a common cold. However, RSV can also cause severe infections in the elderly[11]	▪ RSV associated diseases are curable, and length of disease episode is moderate enough to exclude a significant impact on QoL of informal carers[5]	▪ Among the elderly, RSV infection has a significantly higher risk of death compared to seasonal influenza[11]	▪ The most severe RSV infections are among the retired elderly[11]	▪ Productivity of carers may be impacted because the most severe RSV infections requiring care occur among the elderly[5]
Escherichia coli infection	Adults	▪ E. coli infection symptoms include stomach cramps, diarrhoea and vomiting. Most infections get better in 5-7 days, but more	▪ The length of E Coli infections episodes is typically moderate enough to exclude a significant impact on QoL of informal caregivers[5]	▪ E. Coli may lead to life-threatening complications in children, the elderly and immunocompromised individuals[12]	▪ Severe episodes of E. Coli may require hospitalisation periods that require time off work, or cause chronic disabilities[12]	▪ Treatment of severe cases takes place in hospital, hence impact on carers' productivity is unlikely to be significant[5]

DISEASE	POPULATION	VALUE ELEMENTS 1				
		Impact on QoL of patients	**Impact on QoL of carers**	**Impact on length of life**	**Impact on patient productivity**	**Impact on carer productivity**
		severe ones can be life-threatening[12]				
Meningococcal infection	Children	▪ The majority of patients recovers completely but aggressive forms of meningitis can leave survivors with long term disabilities[13]	▪ Parents suffer mental distress when their children become and in the long-term when their children survive with impairing sequelae[13]	▪ Meningitis is a potentially life-threatening disease[13]	▪ Productivity losses may be due to premature death and long term disabilities[14]	▪ Carers of children with meningitis will incur productivity losses during the hospitalisation period and subsequent check-ups[15]
Varicella zoster virus infection	Children	▪ Chickenpox in children is responsible for fever and low energy levels[16]	▪ Chickenpox episodes are of moderate length, thus not affecting significantly carers QoL of carers expected[5] ▪ Caregiving burden due to herpes zoster in adults is limited[5]	▪ Risk of death is higher among immunocompromised children and adults, but low otherwise[17]	▪ Varicella impact on quality of life is unlikely to have implications for the long-term productivity of patients[5]	▪ Parents may miss a few days of work to attend a sick child with chickenpox[5]
Breast cancer	Adult	▪ At diagnosis, patients may suffer mental distress, and during chemotherapy they	▪ Breast cancer caregivers' may also be affected by mental	▪ Five-year survival rates vary to a significant degree: from 99% for diagnosis at stage one	▪ Breast cancer can lead to premature mortality,	▪ Caregiver involvement in household activities may increase as a result of the patient's

DISEASE	POPULATION	VALUE ELEMENTS 1				
		Impact on QoL of patients	**Impact on QoL of carers**	**Impact on length of life**	**Impact on patient productivity**	**Impact on carer productivity**
		may experience fatigue and pain[19] ▪ In the post-treatment stages, patients' mental health may be affected by fear of recurrence[19]	distress and depression[20]	disease to 15% for diagnosis at stage four disease[21]	work absenteeism and premature retirement[22]	disease, thus decreasing caregiver work productivity[23]
Diabetes, Type 2	Senior	▪ Diabetes type 2 is treated with regular medication but may lead to severe complications, such as renal failure, coronary arterial disease, blindness[24]	▪ Caregivers of type 2 diabetes may be more likely to have depression[25]	▪ Diabetes type 2 complications may impact patients' length of lie, but a timely diagnosis and effective management patients can achieve normal life expectancy levels[26]	▪ Evidence of absenteeism, disability and premature retirement of patients approaching the retirement age[27]	▪ Impact on productivity of carers likely to increase with the risk of complications and patient's age[5]
Prostate cancer	Adult	▪ Prostate-cancer and its treatment can impact quality-of-life domains related to urinary, sexual, bowel, and hormonal function[28]	▪ Prostate cancer and its treatment can cause spousal distress and dissatisfaction with the treatment outcome[28]	▪ High rates of 5-year survival rate in the UK, but higher mortality rates with more aggressive or later diagnosed cancers[29]	▪ Prostate cancer incidence higher in non-working patient population, aged 75-79 years[29]	▪ Caregiver involvement in household activities may increase as a result of the patient's disease, thus

DISEASE	POPULATION	VALUE ELEMENTS 1				
		Impact on QoL of patients	Impact on QoL of carers	Impact on length of life	Impact on patient productivity	Impact on carer productivity
						decreasing caregiver work productivity[23]

Notes: [1] (Engelhard et al., 2018); [2](Marc et al., 2011); [3](Trickey et al., 2017); [4](Verbooy et al., 2018); [5]Expert judgement; [6](Hollmann et al., 2013); [7](WHO, 2018b); [8](Fragaszy et al., 2018b); [9](Luengo-Fernandez, Leal and Gray, 2010); [10](Rees, O'boyle and MacDonagh, 2001); [11](CDC, 2018a); [12](WHO, 2018a); [13](Olbrich et al., 2018); [14](WHO, n.d.); [15](Chen et al., 2019); [16](Gershon et al., 2015); [17](CDC, n.d.); [18](Bilcke et al., 2012); [19](Paraskevi, 2012b); [20](Gorji et al., 2012); [21](Cancer Research UK, 2017c); [22](Frederix et al., 2013); [23](Kamal et al., 2017); [25](Anaforoğlu et al., 2012); [26](Diabetes.co.uk, 2019); [27](Breton et al., 2012); [28](Sanda et al., 2008); [29](Prostate Cancer Foundation, n.d.)

Table B2: Value assessment results (2)

DISEASE	POPULATION	VALUE ELEMENTS 2				
		Burden of disease	**Enablement Value**	**Transmission value**	**Prevent the development of AMR**	**Cost-offsets to healthcare system**
HIV	Adults	▪ Sum of burden of HIV disease and HIV complications amounts to 0.1% of total DALYs lost in the UK[1]	▪ Untreated HIV will damage the immune system thus compromising the treatment of other diseases (e.g. chemotherapy for cancer), but currently it is possible to treat HIV with antivirals[2]	▪ HIV is transmitted via certain body fluids from infected individuals[3]	▪ HIV is a viral disease, not associated to antibiotic use[2]	▪ Risk of disease complications related to impairment of immune system may require hospitalisation[2]
Influenza	Children, Adults	▪ In 2009-2013, influenza was responsible for 29.8% of the total number of DALYs lost in Europe[4]	▪ Influenza is unlikely to cause complications in children and adults that prevent the treatment of diseases associated to other comorbidities[2]	▪ Transmission of influenza can be high in certain seasons of the year, typically winter[5]	▪ Episodes of influenza are associated to inappropriate prescription of antibiotics[6]	▪ Risk of hospitalisation is higher among weaker patient groups, but outpatient costs are also high[7]
Alzheimer	Adults	▪ Alzheimer ranks 5th among the diseases responsible for the highest percentage of	▪ Alzheimer is unlikely to compromise the immune system of patients to the point of preventing the	▪ Alzheimer is a non-communicable disease[2]	▪ Alzheimer is a non-communicable disease, not	▪ Need of medical care and social services increase in the late stages of the disease[8]

DISEASE	POPULATION	VALUE ELEMENTS 2				
		Burden of disease	**Enablement Value**	**Transmission value**	**Prevent the development of AMR**	**Cost-offsets to healthcare system**
		DALYs lost in the UK (3.46%)[1]	treatment of other diseases[2]		associated to antibiotic use[2]	
Respiratory syncytial virus (RSV) infection	Adults, Senior	▪ RSV is one of the leading causes of lower respiratory tract infections (bronchiolitis and pneumonia), which are among the top 5% diseases with the highest burden of disease in the UK (2.11%)[1]	▪ Due to the lack of treatment for RSV, severe infections in the weaker population groups may prevent the treatment of disease associated to other comorbidities[2]	▪ RSV infections are transmitted via coughs or sneezing from infected people [9]	▪ Even though the rates of bacterial infections complicating RSV are rare, antibiotics are often prescribed in children with viral RSV bronchiolitis[10]	▪ Greatest source of use health resources due to RSV infection is from outpatient visits[11]
Escherichia coli infection	Adults	▪ E. Coli is one of the multiple causes of diarrheal diseases, which overall are 0.22% of the total DALYs lost in the UK[1]	▪ Resistant E. Coli infections for which antibiotics do not work may prevent surgeries in patients with compromised immune systems[2]	▪ E Coli is transmitted to humans primarily through consumption of contaminated foods[12]	▪ E. Coli is listed in the 'critical' group of the WHO priority pathogens list[13]	▪ E. Coli infections can result in physician visits, emergency department visits and hospitalisation[14]
Meningococcal infection	Children	▪ The sum of burden of meningococcal disease and related complications is about	▪ A meningococcal vaccine is required before starting treatment for	▪ Meningitis can be spread by contact with infected people[15]	▪ Many of the bacteria included in the list compiled by WHO can	▪ Short- and long-term medical cost of meningitis disabilities

DISEASE	POPULATION	VALUE ELEMENTS 2				
		Burden of disease	**Enablement Value**	**Transmission value**	**Prevent the development of AMR**	**Cost-offsets to healthcare system**
		0.08% of the total DALYs lost in the UK[1]	haemolysis and thrombotic microangiopathy[24]		cause bacterial meningitis[16]	from severe cases are large[17]
Varicella zoster virus infection	Children	▪ Burden of varicella and herpes zoster is about 0.02% of total DALYs lost in the UK[1]	▪ Varicella and herpes zoster are unlikely to prevent the treatment of other diseases in the affected patient[2]	▪ The virus spread via close contact with infected people[18]	▪ Varicella zoster infections are viral and not associated to antibiotic use[2]	▪ Varicella can result in significant burden to the health system in terms of physician visits and hospitalisation[19]
Breast cancer	Adult	▪ Breast cancer ranks among the top-10 diseases for number of DALYs lost in women in the UK[20]	▪ Systemic cancer treatment is likely to compromise the immune system of patients to the point of preventing the treatment of other diseases[2]	▪ Breast cancer is a non-communicable disease[2]	▪ Breast cancer is not associated to antibiotic use[2]	▪ Medical costs of breast cancer increase with the disease stage at diagnosis[21]
Diabetes, Type 2	Senior	▪ Diabetes is in the top 5% of diseases responsible for the largest DALYs loss in the UK (2.32%)[1]	▪ Diabetes complications, particularly among the elderly, may prevent	▪ Diabetes is a non-communicable disease[2]	▪ Diabetes is not associated to antibiotic use[2]	▪ Diabetes accounts for about 10 per cent of the NHS budget and 80 per cent of these costs

DISEASE	POPULATION	VALUE ELEMENTS 2				
		Burden of disease	**Enablement Value**	**Transmission value**	**Prevent the development of AMR**	**Cost-offsets to healthcare system**
			the treatment of other comorbidities[2]			are due to complications[22]
Prostate cancer	Adult	▪ Prostate cancer is in the top 10% of diseases responsible for the largest burden of disease in the UK (1.06%)[1]	▪ Systemic cancer treatment is likely to compromise the immune system of patients to the point of preventing the treatment of other diseases[2]	▪ Prostate cancer is a non-communicable disease[2]	▪ Prostate cancer is not associated to antibiotic use[2]	▪ Prostate cancer is associated with increased direct healthcare costs over the natural history of the disease. Costs are highest around cancer diagnosis and cancer death[23]

Notes: [1](IHME, 2017); [2]Expert judgement; [3](WHO, 2019); [4](Cassini et al., 2016); [5](WHO, 2018b); [6](Havers et al., 2018); [7](Federici et al., 2018); [8](Castro et al., 2010); [9](CDC, 2018a); [10](Quintos-Alagheband et al., 2017); [11](Amand et al., 2018); [12](WHO, 2018a); [13](Tacconelli et al., 2017); [14](Frenzen et al., 2005); [15](NHS, 2019); [16](Meningitis Research Foundation, 2018); [17](Wright, Wordsworth and Glennie, 2013); [18](CDC, n.d.); [19](Brisson and Edmunds, 2003); [20](Steel et al., 2018); [21](Sun et al., 2018); [22](Diabetes UK, 2014); [23](Krahn et al., 2010),[24] (NICE, n.d.)

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