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The role of epidemiology research in economic evaluation for Health Technology Assessment

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ABSTRACT

The need for economic evaluation of new health care technologies, especially in the modern world era, is undisputable. Economic evidence alongside clinical evidence are the two main pillars of the Health Technology Assessment (HTA), a process which is followed for reimbursement medical technologies and budget allocation decisions. The role of epidemiological research is essential in obtaining the necessary data for the development of the economic evaluations. In this review paper, we adopt a stepwise approach, based on current guidelines for conducting economic evaluation (both budget impact and cost effectiveness analyses) for highlighting the need for modern epidemiological methods and tools in such a process. Epidemiological studies provide the data for the eligible patient population, the prevalence and incidence of disease, treatment effectiveness and health care resource utilization; these, in turn, are synthesized in an appropriate framework, together with real world data, for assisting in the budget allocation decisions.

KEY WORDS: *Epidemiology, health economics, health technology assessment, evidence, real world data*

BACKGROUND

In the real world the demand for health care is increasing, where the introduction of new and, in many cases, expensive therapies, is rapid[1]. In addition, societies grapple with additional health care costs, especially when emerging health situations, like the COVID-19 pandemic, arise, in parallel with scarce health care resources. Thus, the need for appropriate health care budget allocation to maximise population health is more pertinent that it has ever been. The planning of the health care expenditure commences with establishing what the available resources are (i.e., overall budget of the health care payor or government), the health care needs of the population, the availability of new treatments to cover the unmet needs and, finally, the allocation of the resources in different treatments and disease areas. New treatments are reimbursed, hence allocated resources to, by the health care payors upon the complete clinical and economic evaluation, which are parts of HTA process of the new medical technologies for reimbursement decision purposes.

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ABBREVIATIONS: *BIA: Budget impact analysis, CEA: Cost-effectiveness analysis, HCRU: Health Care Resource Utilisation, HTA: Health Technology Assessment, ISPOR- International Society for Pharmacoeconomics and Outcomes Research, NICE: National Institute for Health and Care Excellence in the UK, QALYs: Quality adjusted life years, RCTs: Randomised controlled trials, RWE: Real world evidence, RWD: Real-world data*

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The HTA definition has evolved over the years to capture all the developments of the science and practice of HTA. Currently, HTA is defined as a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. Its purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system[2]. The "value"" of a health technology assessment is determined by a number of dimensions, mainly the clinical effectiveness of the health technology, safety, costs and economic implications. A variety of other parameters such as ethical, social, cultural and legal issues, organizational and environmental aspects, as well as wider implications for the patient, relatives, caregivers, and the population are taken into account in the deliberative process of the HTA[3].

Economic evaluation, one of the most important pillars of the HTA, is "*the comparative analysis of alternative courses of action in terms of both their costs and their consequences*"[4]. For a complete economic evaluation, cost-effectiveness and budget impact analyses have been proposed as the most efficient methodologies for decision making. Specifically, the cost-effectiveness analysis (CEA) examines whether the new treatment benefits outweigh the related adverse events and costs, and whether the ratio of the additional cost over the additional benefit falls within acceptable, to the health care payor, ranges. The benefits are measured in natural units, such as life-years gained, in preference-based outcomes, such as quality adjusted life years (QALYs) or in monetary terms (i.e., net benefit). The budget impact analysis (BIA) examines the changes in the overall budget due to the adoption of the new treatment and its overall affordability from the perspective of the health care payor. Both analytical tools (i.e., CEA and BIA) are the foundation of HTA, a process which has been followed in many countries for the reimbursement of new drugs for over the past years. The economic assessment of new drugs creates the methodological space where the economics meet the medical science.

The role of the epidemiological research in health services, planning, and health care budget allocation is a topic which has been thoroughly discussed in the literature[5], following the rise of the health economics as a discipline. The value of epidemiology has undoubtedly been recognised as a vehicle for advancing the study designs of the health services, as well as for acquiring those data that are vital for the application of health economics and the relevant decision making. In this paper we aim to review those points which delineate the role of epidemiology research in relation to economic evaluation, under the context of real-world data (RWD) and evidence (RWE). The application of the epidemiology in economic evaluations will be unfolded as a stepwise approach, which mirrors the recommendations in the relevant guidelines for the conduct of both CEA[6,7,8] and BIA[9].

How can epidemiological research help to understand the real world?

Traditionally, epidemiology is "the study of the distribution and determinants of disease frequency in human populations"; however, there is a constant evolution in the definition and the role of epidemiology[10]. Current definition states that "modern" epidemiology is the study of the distribution and determinants of health-related states or events (including disease), and the application of this study to the control of diseases and other health problems[11]. Epidemiological research toolset possesses an armoury of techniques which are utilised for collecting, analysing and improving the data from a variety of study designs, natural settings and sources. A typical example of use of epidemiological methods is their utility in generating RWE from RWD. The dramatic increase of information technologies uses during the past years, like internet, social media, wearable devices, cloud storages, networks, and other electronic services, has led to the rapid generation of huge amounts of digital data that are now counted to exabytes or even zettabytes. In addition, health insurance claims and billing activities, hospital and pharmacy records, product-specific and disease registries, can also assist in gathering real-world data (RWD) that are essential for an evidence-based decision making.

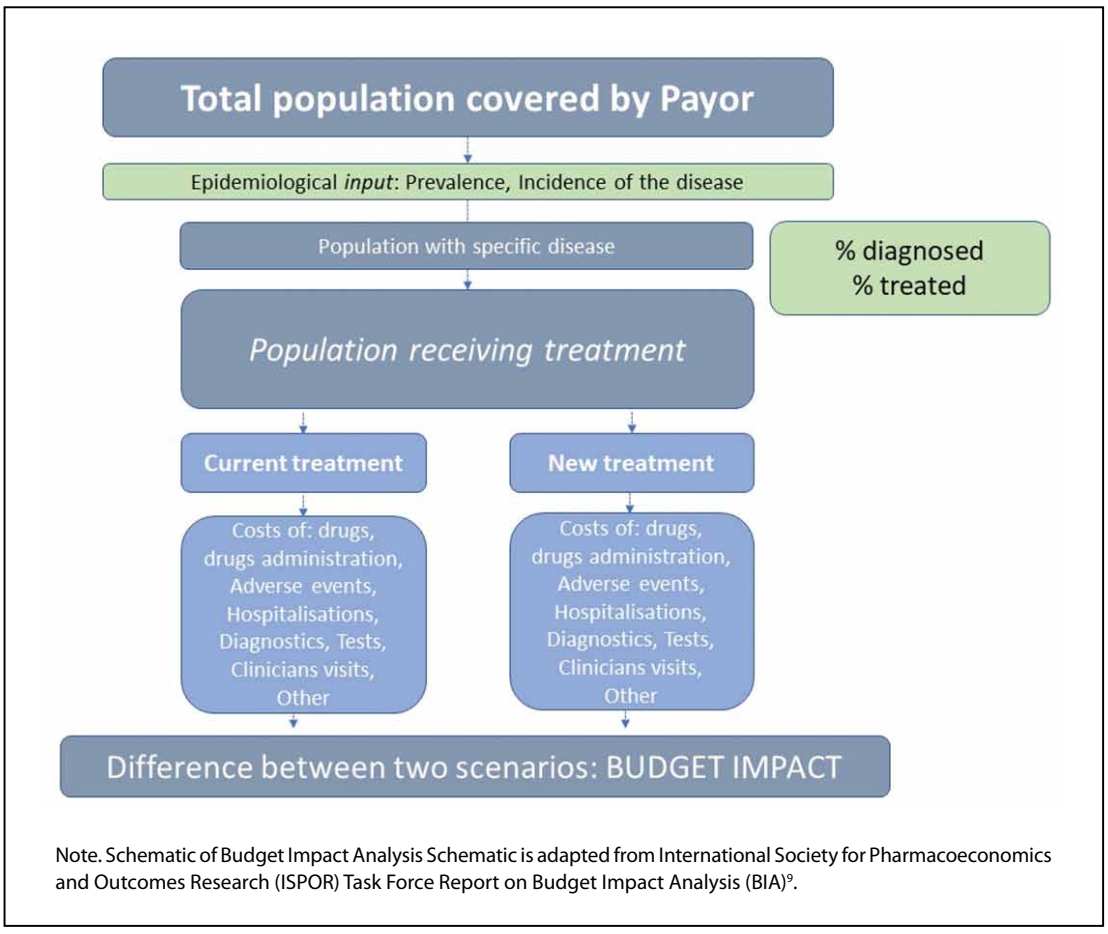
RWD have several similarities as compared to the data collected from epidemiologic studies. In particular, RWD are observational, similar to the data gathered in an epidemiological setting. Hence, they share the same limitations driven by the observational nature of the data. Moreover, many types of RWD are unstructured and inconsistent because of the variety of sources and ways of synthesising them. In some cases, the RWD are unrepresentative of the underlying population. Epidemiology can substantially assist in improving the quality of RWD. Several epidemiological methodologies have been developed to account for the various types of bias, to ensure representativeness of sampling, to reduce errors in measurements, etc; these methodologies can also assist in building more robust vehicles for collecting RWD such as hospital and pharmacy records, product-specific and disease registries, and other sources of RWD[12]. Furthermore, the fast development of data analytics techniques, like machine learning and artificial intelligence, together with the statistical methodologies have created great interest in the use of RWD to bridge the gap between medical research and daily practice.

How can epidemiological evidence be integrated into an economic evaluation?

It has been acknowledged that epidemiology and health economics have several systemic interdependences, and quite often epidemiologic-economic models are used as an analytical platform for developing CEA and BIA. There are a few important steps in the development of the BIA, as recommended by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force Report[7] and are captured in Figure 1. The figure captures the comparison, in terms of budget impact, of two environments: the current and the future environment where the new treatment has been introduced in the clinical practice. The impact of the new treatment is measured on several variables, such as the reduction of the disease cases, in the case of preventive interventions, as well as impact on overall all health care resource usage such as hospitalizations, clinicians' visits and additional treatments required for the management of the disease. The difference in costs between the two environments provides the overall budget impact of the new treatment.

Identification of the eligible population for economic evaluation

The development of both BIA and CEA commences with the identification of the target or eligible population for the new treatment. In epidemiology, the target population is "the defined group of diseased persons for whom the effect of a particular procedure or therapy is to be determined by the way in which it alters the natural history of the disease"[13]. Further, the target population can be divided into subgroups of patients defined by disease severity or stage, comorbidities, age, sex, ethnicity, and other characteristics, which is the type of information that falls within the realm of epidemiology. As an example, let us use the case of a drug which has been created for a type of cancer which develops only in those individuals that bear a specific type of gene mutation. For the budget holder (e.g., national health services or insurance companies) to establish whether the new treatment is "affordable", hence can be reimbursed, the analysis must identify the number of the patients with the specific disease/mutation from the total population which is covered at a specific point



Note. Schematic of Budget Impact Analysis Schematic is adapted from International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force Report on Budget Impact Analysis (BIA)[9].

FIGURE 1. Schematic of Budget Impact Analysis.

in time by the budget holder. The cascade of numbers starting from the total population, covered by a health care payor, to the patients with the specific type of cancer within that population (prevalence of the disease), which is then narrowed down to the number of patients with the gene mutation (prevalence of the mutation within the disease) results from epidemiological studies. Prevalence is an epidemiological principle which is measured typically through a cross-sectional study design . These studies are observational in nature and provide a snapshot of the number of patients with a specific disease at one point in time.

It should be mentioned here that the difference of the definition of "eligible population" between CEA and BIA is that the former refers to the individual, with specific characteristics, where the latter to the cohort which is the total number of individuals with specific characteristics. Nevertheless, the identification of the target population relates to identifying and describing the patient(s) with a very specific set of characteristics, for whom the new treatment has been developed and assessed.

In addition to prevalence, the incidence of the disease is an important measure which is often used in the BIA. The time horizon of a BIA can usually be longer than one year, typically 3 to 5 years, which fits with budget planning of the budget holder. Hence, it is important to measure the impact of the new treatment or intervention (e.g., screening for the gene mutation, hence prevention of the cancer in our example above) from one year to the next and account for the increase/decrease of the target population due to the change in the incidence of the disease. Since causation is important in this case, and the numbers are not affected by subsequent deaths, then a follow-up of patients over time is required and is usually achieved through patient registries[14]. This is another important study design in the armoury of epidemiological tools which is utilised for budget planning purposes. Furthermore, as we will discuss below, registries provide real world data for assessing the effectiveness of the new treatments in the real-world setting and enhance the case for cost-effective allocation of budget on treatments past their approval stage[15].

Treatment effectiveness and economic evaluation

One of the important pillars of economic evaluation is the assessment of the effectiveness of the competing interventions. Different types of research designs, all of which are part of the experimental epidemiological "toolset", are employed for the assessment of the effectiveness at the various stages for the product development. Clinical epidemiology is a broad field, which cover topics such as outcomes measurement, evaluative testing, descriptive studies of disease course and outcomes, and studies of interventions. However, for assessing the treatment effectiveness, randomised controlled trials (RCTs) are considered as the highest grade evidence[16] compared to observational studies. Random allocation ensures that all treatment groups are balanced, except for chance differences, with respect to all known and unknown covariates that might affect outcome. This powerful design enables the researcher to be confident that any differences between treatment groups are due to the intervention under evaluation rather than some alternative explanation for any treatment effects.

For reimbursement purposes, economic evaluations are usually conducted alongside the Phase III RCT, where the relevant comparator in the clinical trial is the same as the one in the current clinical practice; however pragmatic effectiveness trials are considered the most appropriate epidemiological research tool for economic evaluation at post-marketing stage as they provide data from real world setting[2], without the artificial restrictions of the Phase III efficiency trials. This enhances the generalisability and the external validity of the findings. Although there are differences in the implementation of these study types, the epidemiological design principles remain the same.

The value of real-world evidence in economic evaluation

In the recent years there is an increasing recognition of the value of real-world evidence (RWE)[13], which clearly reflects data used for decision-making that are not collected in a conventional setting, like RCTs or epidemiological studies. For example, the National Institute for Health and Care Excellence in the UK (NICE), a worldwide leading authority and methods innovator for health technology assessment[17], mentions the use of both "non-randomised and non-controlled evidence", such as observational studies, and "indirect comparisons and network meta-analyses" for comparing technologies that have not been compared in direct, head-to-head RCTs[18,19]. Further, in practice the same organisation has proceeded with the approval of products based on single arm, Phase II trials[20] based on the rationale of innovative technologies and high unmet clinical need. However, the approval is conditional on further data collection to account for the uncertainty in outcomes stemming from the design of the clinical trial[21] - hence, RWE is used both during the initial appraisal and reappraisal of the products, upon collection of additional evidence. The use of non-randomized trials is also used in cases when the randomization is not possible. Epide-

miologic methods assist with enhancing the validity of the findings from analysis of RWD which, as mentioned, bear several limitations.

Estimation of health care resource utilisation

As discussed previously, treatment effects as well as prevalence and incidence of the disease constitute epidemiological data which are key components of economic evaluation. Further to this, the direct and indirect costs, which comprise the other important element of the economic evaluations, are estimated based on the quantities of the Health Care Resource Utilisation (HCRU) in routine practice. Insurance claims and administrative databases, patient registries, and databases of hospital statistics are used for collecting national data on HCRU, alongside the self-reported, patient-level data collected in RCTs or data collected via cost diaries . These are only a few examples which fall in the realm of epidemiological methods for identifying, extracting, analysing, and utilising data from secondary sources for research purposes.

Extrapolation of trial results beyond trial duration

The data and conclusions derived from the RCTs are only applicable for the trial duration, which is usually short (e.g., 3-5 years). Quite often, the benefits of new treatments extend beyond the trial duration, and policy decision makers most commonly are interested in long-term effects of new interventions for budget allocation purposes. Hence, it is important that the long-term treatment effects, which are incorporated in economic evaluations, are estimated as accurately as possible for a longer timeframe, usually lifetime horizon (as recommended by HTA agencies)[16,17]. This is achieved by extrapolation of the trials' results through modelling methods[22] . For example, for cancer treatments that improve the survival outcomes, these are extrapolated beyond the trial duration via survival models. An important step in the choice of clinically plausible survival models, is the assessment of the validity and credibility of the extrapolations[23]. For this purpose, external data sources with longer term data, such as other trials, disease (cancer) registries, general population mortality rates, and national life-tables, published by national statistics authorities, all of which are epidemiological tools, are utilised.

Epidemiological modelling as a platform for economic evaluation

As alluded in the previous paragraph, many economic evaluations involve some type of economic modelling to extrapolate the results of RCTs in the longer time-horizon. Importantly, the economic modelling is primarily used to synthesize cost and outcome data from various, fragmented sources in absence of head-to-head comparisons of competing interventions, as it is the case with economic evaluations alongside clinical trials. The use of modelling techniques is a shared practice between health economics and epidemiology, since mathematical modelling in epidemiology finds applications in public health policy and cost-effectiveness analyses[24]. There are various categories of epidemiological models, depending on the treatment of uncertainty (deterministic or stochastic), time (continuous or discrete intervals), transmissibility of the disease (dynamic or static), space (non-spatial or spatial), and the structure of the population (population vs. individual based). However, the fundamental principles remain the same: epidemiological modelling creates a simulated and simplified version of the real world, which when parametrised accordingly, is used to understand the impact of the disease and/or intervention(s). In other words, epidemiological models synthesize complex information and evaluate the significance of model's inputs, in a simplified way to forecast outcomes of alternative courses of actions for policy making purposes[25]. Epidemiological models are built in lieu of the natural experiments to test hypotheses, since for many diseases, whether communicable or non-communicable, conducting trials is quite often impossible, unethical, or time and resource intensive.

Epidemiological models create the perfect platform for economic evaluation. Depending on the type of the disease (communicable or not) and the modelling approach adopted, as outlined above, the disease epidemiological model will typically incorporate various health states (e.g., susceptible, infected, diagnosed, ailing, healed, dead). These are used as the backbone of the economic analysis, where the HCRU and respective unit costs can be assigned to model states, to calculate total costs of competing interventions, alongside the clinical outcomes[26].

The characteristic example of applications of these models are the epidemiologic-economic models of infectious diseases or those of vaccinations' effects. Very recent examples include the public policy decisions for COVID-19 response which are based on models that jointly assess economic and epidemiological data[27]. Most of these studies use epidemiological models to estimate the number of death and hospitalisations due to COVID-19 under different policies to control the disease. Although experiments with infectious disease spread in human populations are often impossible, unethical or expensive, the recent pandemic provided the real-world data which prompted epidemiologists around the world to explore and produce disease models of this pandemic. These models helped guide policy decisions on measures for

combating the spread of COVID-19, while assessing the wider costs and benefits to the society as a whole (economic, humanitarian, psychologic, educational, etc) of such measures[28].

CONCLUSIONS

In this paper a stepwise approach was adopted to describe the use of epidemiological data for economic evaluation purposes, which is component of health technology assessment and budget allocation decisions. The methods and the data which are collected via epidemiological research tools constitute a vital part of the economic analyses. Epidemiology tools help transform the RWD into usable RWE for policy making purposes, via appropriate designs, data analysis and improvement. Epidemiologic modelling is the backbone of economic evaluation, since it represents complex disease stages in a simplified way. The interdependence of the two disciplines, epidemiology and health economics, is an undisputable fact. The cross-collaboration of the scientists in designing epidemiological studies that satisfy the needs of health economics analyses is vital for successful research which can provide a great benefit to the research community and the society as a whole.

Ethics Approval and Consent to Participate

Not applicable, as this is a review paper

Conflict of Interest

None to declare.

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ΠΕΡΙΛΗΨΗ

Ο ρόλος της επιδημιολογικής έρευνας στην οικονομική ανάλυση για Αξιολόγηση Τεχνολογιών Υγείας

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Η ανάγκη για οικονομική αξιολόγηση των νέων τεχνολογιών υγείας είναι αδιαμφισβήτητη. Η Αξιολόγηση Τεχνολογιών Υγείας (ΑΤΥ) είναι η επίσημη διαδικασία που ακολουθείται για την αποζημίωση τεχνολογιών υγείας και για αποφάσεις κατανομής χρηματικών πόρων στο σύστημα υγείας. Τα οικονομικά και κλινικά στοιχεία είναι οι δύο βασικοί πυλώνες της ΑΤΥ. Ο ρόλος της επιδημιολογικής έρευνας είναι ουσιαστικός για την απόκτηση των απαραίτητων δεδομένων που χρησιμοποιούνται στις οικονομικές αξιολογήσεις. Η σύντομη αυτή ανασκόπηση βιβλιογραφίας κάνει χρήση των τρεχουσών κατευθυντήριων οδηγιών για τη διεξαγωγή οικονομικών αξιολογήσεων (τόσο αναλύσεων επίπτωσης στον προϋπολογισμού, όσο και αναλύσεων κόστους-αποτελεσματικότητας) για να αναδείξει την αναγκαιότητα για σύγχρονες επιδημιολογικές μεθόδους. Οι επιδημιολογικές μελέτες παρέχουν τα δεδομένα για τον επιλέξιμο πληθυσμό ασθενών, τον επιπολασμό και τη συχνότητα εμφάνισης της νόσου, την αποτελεσματικότητα θεραπειών και τη χρήση των πόρων υγειονομικής περίθαλψης. Τα στοιχεία αυτά, με τη σειρά τους, συντίθενται σε ένα κατάλληλο πλαίσιο ούτως ώστε να διεξαχθούν οι οικονομικές αναλύσεις προς χρήση στη λήψη αποφάσεων για την αποζημίωση νέων τεχνολογιών υγείας.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: *Επιδημιολογία, οικονομικά της υγείας, αξιολόγηση τεχνολογίας υγείας, τεκμήριο, δεδομένα πραγματικού κόσμου*

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