THE 1ST INTERNATIONAL WORKSHOP ON INNOVATIVE SIMULATION FOR HEALTH CARE

SEPTEMBER 19-21 2012

VIENNA, AUSTRIA

EDITED BY

WERNER BACKFRIEDER

AGOSTINO BRUZZONE

FRANCESCO LONGO

VERA NOVAK

JOSEPH ROSEN

PRINTED IN RENDE (CS), ITALY, SEPTEMBER 2012

ISBN 978-88-97999-05-8 (Paperback)
ISBN 978-88-97999-13-3 (PDF)

ISBN 978-88-97999-05-8 (Paperback)
ISBN 978-88-97999-13-3 (PDF)

IFEDH - SOLVING HEALTH SYSTEM PROBLEMS USING MODELLING AND SIMULATION

Niki Popper[(a)], Ingrid Wilbacher[(b)], Felix Breitenecker[(c)]

[(a)]dwh Simulation Services, Vienna, Austria
[(b)]Main Association of Austrian Social Security Institutions, Vienna, Austria
[(c)] Vienna University of Technology, Institute for Analysis and Scientific Computing, Vienna, Austria

[(a)]niki.popper@drahtwarenhandlung.at, [(b)]ingrid.wilbacher@hvb.sozvers.at, [(c)]felix.breitenecker@tuwien.ac.at

ABSTRACT

Health Technology Assessment (HTA) is used to inform decision makers on the level of the health care system or at the population level. The consortium IFEDH (**I**nnovative **F**ramework for **E**vidence based **D**ecision support in **H**ealth care) was formed to invent a new strategy to integrate modelling and simulation into the process of HTA, which deals with limited resources and upcoming new technologies. Dynamic and static modeling is getting more and more essential for this process. Simulation can help decision makers to compare various technologies comparing different goal functions on a basis of evidence. Most important for this is a reliable and reproducible process of modeling and computing of simulations. We will present the developed fundamental framework which connects the most important areas for getting decision bases: Developing the PICO questions, data acquisition and evaluating of data, developing models and interpreting the results. IFEDH is funded by The Austrian Research Promotion Agency (FFG).

PROJECT

Health technology is one of the fastest growing industries and is of main interest for society concerning all layers of the population. Often resources are bounded and long time effects occur, therefore, decisions regarding strategies influence the healthcare policy for decades. Modeling and simulation as a tool for decision-making support is necessary to compute various scenarios. Because of these reasons the idea was to integrate more sophisticated methods of modeling and simulation in the process of HTA.

The main focus of the project lies on the development of these processes, leading an interdisciplinary group of experts in the field of HTA, statistics, modeling, visualization and database analysts through the whole decision support process. Within the last two years the focus was on the application of these methods on infectious diseases simulation and vaccination questions, but the derived methods are directly usable also for all other questions in HTA. Besides the complexity of guiding and controlling the coupling of different scientific domains to realize a joint overall approach in model based HTA, in all sections new approaches had to be developed and implemented.

As decision support has to become faster, parameter sources and modular reusable model parts have to be developed in advance. But the modeling process and the design of adequate modeling methods are only one (core) part. Besides this, the model and parameter validation as well as verification of the developed and implemented system are in focus. The data quality assessments as well as the outcome visualization and interpretation are set up interdisciplinary, ensuring the necessary project quality and acceptance on the part of policymakers.

Scientific Partners in the project are Main Association of Austrian Social Security Institutions, Ludwig Boltzmann Institute for Health Technology Assessment, Vienna University of Technology (VUT) and VRVis Zentrum für Virtual Reality und Visualisierung Forschungs-GmbH, company partners are dwh Simulation Services, E.I.S. Ltd. Florian Endel and FWD GmbH. UMIT- Private University of Health Sciences, Medical Informatics and Technology-GmbH is an additional contributor.

The first step in the project was the analysis of model know-how and structural know-how as well as gathering the state of the art of modeling in HTA in Austria.

Based on this information a specification of requirements regarding model structure and documentation of simulation outputs was set up.

The third step, representing one of the core working tasks of the network was the development of adequate/reusable modeling structures and modeling methods. Therefore an evaluation table of methods in use as well as modeling and simulation strategies from other domains with a potential use in HTA was acquired.

Furthermore modular model parts were developed and tested for their reusability. The analysis of data sources depending on each module as well as the realization of usability tables and interface descriptions finalized this task, ensuring high flexibility and

reusability. Based on this exploratory work was made on:

- different modeling techniques of infectious diseases (Zauner, Popper, Breitenecker (2010)),
- herd immunity effects of population groups using agent based modeling methods (Miksch et al. (2010)) and
- work of IFEDH members on serotype behavior modeling for infectious diseases and vaccination strategies (Zauner et al. (2010))

Based on this research recommendations for good practice were developed.

In act with the evaluation and integration of classical HTA methods, their development for data preparation and analysis with respect to Austrian reimbursement data a ”good practice” manual was realized. The elaboration of standardized visualization concepts for

1. model parameters,
2. model structures and
3. the results,

together with research on scenario set up and sensitivity analysis workflow were integrated and tested for practical use, by implementation of three real world HTA questions.

At the beginning of the IFEDH research project stood the evaluation of the status quo acquired by the following tasks:

1. Documentation of standards in modeling and simulation in the field of health technology and health system evaluation
2. Documentation of standards in HTA: the documentation describes the standard process in vaccination program evaluation as well as the used methods and their limitations. This task is realized using expert opinions and a structured questionnaire to get the state of the art in Austria and neighbouring countries.
3. Documentation referring to identified problems with representation of solution pathways: The document lists the open questions, which appeared in earlier projects of partners using modeling and simulation for evaluation of vaccination scopes. For each problem the used solution strategies and the discussion about general use of this strategy are documented.

Based on this first step the second one was defined and realized: Definition of demand profiles regarding modeling and simulation in HTA.

As the whole process and the resulting service is developed necessarily by interdisciplinary partners, who have to work and understand each other, the definition of a mutual language is a key to success. Therefore a glossary based on international definitions and formulations used by single project partners is realized. To guarantee the actuality, this document is defined as some sort of open document, being expanded during the whole life span of the project by the partners. Inconclusive or “parallel” formulations are discussed by project participants from different domains; the consensus is stringent for all partners.

The compiling of requirements regarding model structure and documentation of simulation outputs are completing the first project phase. The determination of needs helps to ensure an efficient modeling process in which the models subsequently have to be changed only from time to time.

QUESTION

The process of selecting a question for decision making - prioritization - and the balancing of the findings in the broader political context - appraisal – is not covered in this paper in detail. We address how to generate a reasonable question for the modeling process on basis of the PICO question.

To start working on a relevant question usually needs a clarification of the possible decisions, the definition of the population/ condition addressed, the intervention, the comparator and the outcomes of interest. This is the format of the PICO - Population; Intervention; Control; Outcome - question. In this phase of scoping the question has to be formulated with the best possible precision and a first discussion about the feasibility and necessity of modeling has to take place. To understand differences in the process of HTA knowledge of the health care system is necessary. The political decision making process can be visualized in the following way shown in Figure 1.

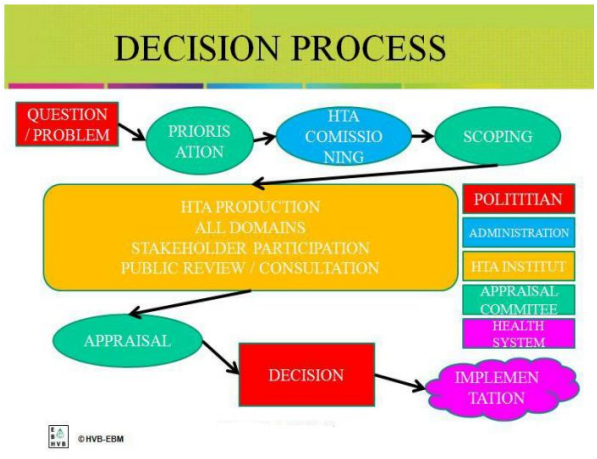

Figure 1: Decision Making Process

Following the PICO question the part of the HTA, which can be subsidized by modeling and simulation has to be specified. The decision which research questions can be answered using models and what is needed for doing this has to be taken. This is done by a

steering group as different aspects are important: The PICO question itself is always the starting point. Based on this data and structure of the problem has to be analyzed. In an iterative process the modeling technique will be developed and – again within the steering group – decided. To be able to handle this process and to guarantee a quality management, a special kind of documentation process was implemented.

DOCUMENTATION

At the end of this process the group has defined an exact definition of "not-model based" HTA questions and the questions which can be handled with methods of modeling and simulation. Based on these questions the modeling process has started and the method decision, as well as the exact specifications of the model were done. At the end the whole parameter and data set, which will be needed to implement the basic simulation as well as all comparative scenarios is defined and communicated within the interdisciplinary team.

On basis of this the process of data acquisition is started. In parallel this process has to be documented reliable and reproducible. IFEDH has developed and described a focused procedure (on basis of the EUnetHTA project and the HTA Core Model) how to describe the process and the status of used data. A web tool – the HTA-Manager - for documentation of source, status and manipulation of data is used

With the HTA-Manager the data needed for all simulation runs (the basic simulation – f.e. the status quo of a given therapy and all possible scenarios - f.e. a new vaccine or new regulatory requirements) can be documented permanently. To make this possible the documentation is done in three steps. The first step is to document the sources for all data sets. There are three different categories of used data: CKAN data, which is one of the world's leading open-source data portal platforms, other open data sets and private or secret data, f.e. data of the insurance associations. After documentation of these sources as step 2 the modification or the adaption of all data sets is documented. These adaptions are f.e. SQL requests, filters or any other modification of the given raw data sets. Step 3 is the download or storage of the used data set for (1) all parameters , for (2) all simulation runs and scenarios into the HTA-Manager. Step 3 is the most important part of the documentation, as with the given data and a full documentation of the model and implementation the simulation runs for the basic system and all scenarios can be reproduced any time any place. This possibility is a main goal of the IFEDH project, to raise the credibility of modeling and simulation within the HTA community.

DATA

Another methodological goal of IFEDH was the development of standards and methods concerning data preparation and data analysis. The aspect of requirements of models referring to data and statistical preparations is under treatment. Concerning the generated model structure definition of requirements on data and their statistical preparations are given. A special effort is put on the necessary quality and the granularity (i.e. how detailed data have to be provided). Again the work is realized in interdisciplinary groups benefiting from results that are comprehensible and usable in a general area.

After identifying the granularity and the data sources a concept of data quality assessment is acquired: The concept explains the data quality assessment that has to be performed using health data including theoretical principles, characteristics concerning health data and information referring to the implementation. The following figure (see Figure 2) motivates the connection and interaction of modeling & simulation, parameterization and data quality assessment. The influence of the quality of data input, parameter estimation and modeling structure (simplifications, unsecure assumptions ...) is discussed in an interdisciplinary manner. In an early project phase the goal is the identification of problems regarding parameterization and the sensitivity of diffuse parameters..

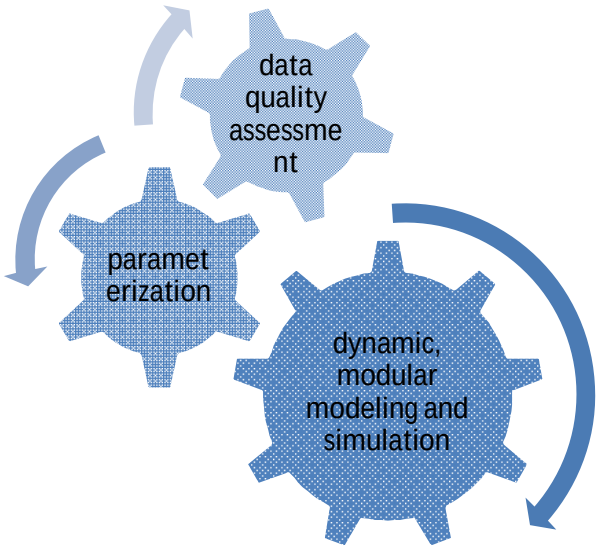

Figure. 2. The connection between dynamic modular models, their parameterization and the data quality assessment is shown.

The influence on the parameterization based on model structure and time intervals simulated is obvious. Furthermore data quality assessment influences the parameterization: Availability of data sources, reliability of parameters and range of confidence interval. Information about missing data quality or even lack of data results are necessary for changes in the model structure or in additional HTA literature work and searching for alternative parameterization attempts. Certainly the model has to fit the real life conditions in an adequate manner. Therefore a consensus in the interdisciplinary group has to be reached in the early project stage. Changes in a later phase generally cause

tremendous additional workload and bring about problems with the decision makers, if changes in the model structure have to be justified.

An important aspect within IFEDH was the usage of routine data in HTA, as gathering data tends to be an expensive and time consuming task. During the IFEDH research project different methods for using routine data on models in HTA were discussed, improved and developed. Connecting a rich dataset from Austrias inpatient sector lacking patient identifiers and (kind of) personalized but sparse records from the outpatient sector provided by different social security institutions is the objective of this project. A detailed description of the setup and usage of the results were presented at the SHIP Conference 2011 in St. Andrews (http://www.scotship.ac.uk/conference-2011) and the International Data Linkage Conference 2012 in Perth (http://www.datalinkage2012.com.au/).

Documentation of prior processing and information of the provided data were not fully available and also questionable data quality and the presence of possible duplicates result in technical and contextual challenges. After prepossessing, data quality assessment and other preparations, a deterministic record linkage approach was developed using a combination of the open and freely available statistical environment R and PostgreSQL database. Based on dynamically created SQL statements and extensive logging, the linkage process can be enhanced easily if new knowledge about the input data gets available.

The resulting linked dataset provides high quality and immediately available information. Additionally the deterministic linkage process can be examined and understood by its users. Therefore linkage and data errors are identified easily and feedback can be used to enhance the overall result. These experiences also lay the foundation for more advanced linkage methods and further improvements.

After the long and challenging way from the first data import to a functioning data collection, adequate information can now be used in different projects with low costs and users confidence.

MODELING

One of the core working tasks of the network is the development of adequate/reusable modeling structures and modeling methods. Modular model parts are developed and tested for their reusability. The analysis of data source depending to each module as well as the realization of usability tables and interface descriptions finalize this task, ensuring high flexibility and re-usability (see Figure 3). Based on exploratory work on different modeling techniques of infectious diseases [1], research on herd immunity effects of population groups using individual based modeling methods [2] and work of IFEDH members on serotype behavior modeling for infectious diseases and vaccination strategies [3] recommendations for new questions are in progress.

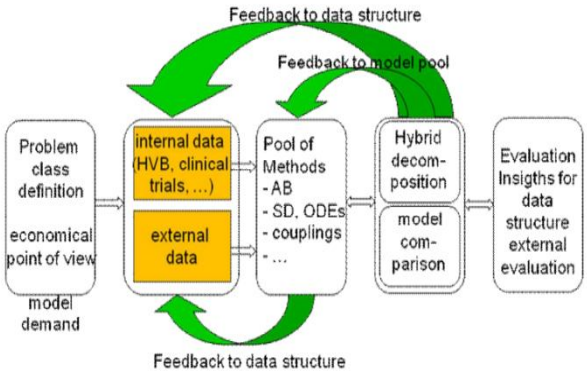

Figure 3: Basic Diagram of model based decision support

First of all, the use of modeling and simulation in HTA is discussed once again to see why this technical approach is used and, furthermore, to identify the raising questions:

- Formulation of the problem:
- What are the questions that shall be answered?
- Concept of the model: Which values are important, which describe the states of the model, which are parameters, which values influence the model in general? Which relations between the values exist?
- Is the model concept useful: Is enough knowledge and data accessible to implement the model? Can the proposed questions be answered using the model if the model assumptions are true?
- Can the model be validated?

Besides the identification of useable modeling methods in answering HTA questions the classification in respect of different points of view is integrated in the description. This classification can help to integrate experts for HTA into the process, even if they are not specialists in modeling and simulation. As classification

- Black-box versus white-box modeling
- Top-down and bottom-up approaches
- Classification representing time

are chosen. Especially the interpretation of differences in top-down and bottom-up modeling techniques as well as explanation of processing of time helps the HTA and data experts to understand what modeling and simulation can perform.

Beyond that the communication regarding how to provide data in usable formats is motivated. This motivation together with an extra task and proof of concept examples strengthen the quality of the developed service by the IFEDH partners.

In case of restrictions of the defined methods that cannot be solved using another method from the first part of the project, combination of different methods has to be discussed. Using this open approach; first defining the HTA questions using a PICO schema and then choosing the modeling methods based on the

research question and information about data structures and expected time behavior is depicted.

The starting point is the definition of the problem/the HTA question. The main important fact in this system is that the data structure analysis is performed before the modeling method is chosen. Nevertheless the modeling process is done iteratively. The hybrid decomposition as well as the comparison of different methods and modular use of pre-developed tasks is part of the new developed concept in the IFEDH research project.

The development of reusable parts of the model and especially the theoretical background is focused. Their advantages and disadvantages, restrictions and potential applications in the field of evaluation of vaccination strategy are discussed. A general framework (see Figure 4) is developed and tested using pre-defined proof of the concept – examples that are processed together by the different partners in IFEDH.

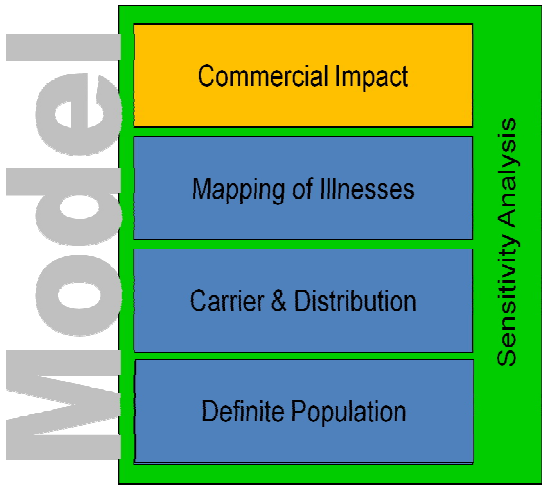

Figure 4. Example for splitting a cost effectiveness. Evaluation of a vaccination program for a given population into modules. The overall modeling concept can be discussed, implemented and parameterized in several reusable blocks.

The necessary question about the context between model and how to get the parameters into the framework is pointed out. To ensure the reliability and the quality of the datasets used following methods are discussed:

- sensitivity analysis – using this method the HTA and modeling experts get knowledge about the overall influence of parameters of interest,
- parameterization and calibration: Calibration is a systematic adjustment of model parameters that are either unknown or uncertain (Taylor, 2007). The strategy is to adjust these questioned parameters in a way so that the model results fit given data sufficiently.
- verification,
- validation, and, finally,
- simulation experiments and scenarios that provide results.

Calibration is a process of setting parameters, running the model, assessing the results, adjusting the parameters based on the results and running the model again. This procedure is performed until the results are satisfying.There are two types of situations that require calibration of a model (Taylor, 2007):

- When data are inadequate or missing to estimate all model inputs.
- When validity of a model is questioned.

The development of hybrid modeling methods and modular model classification in the field of communicable diseases and especially for vaccination questions in HTA together with pointing out the main working tasks for parameterization close this main task of the IFEDH project.

VISUALISATION

The development of standardized visualization methods and representation of results – was integrated in the project to generate additional insight in the model structure, to help explaining the calculated results and also to have a powerful graphical tool for parameterization.

The workload was split into several tasks, whereby the analysis of state of the art methods in HTA was one of the first. Additionally, to think outside the box, adequate visualization methods from other areas were detected and analyzed and also a rating regarding potential use in modeling questions for HTA was done. This rating was directed by the visualization experts together with the modeling group and classical HTA expertise.

The other tasks were mainly based on the data basis for visualization. A guideline for visualization of generally evaluable data basis for vaccination program evaluation and the explorative analysis and visual inquiry of data quality was developed.

For visualization of results, also methods form other application areas were introduced into HTA. Only to name one, parallel sets were integrated as interactive visualization approach for analyzing markov models, as common methods to visualize Markov states over time (e.g., Markov-cycle trees or state probability graphs) do not scale well to many cycles and have limitations concerning the perception of proportions. To overcome these limits new visualization methods of Markov models and their results were investigated, inspired by the “Parallel Coordinates”. An interactive technique called Parallel Sets has been developed for visualizing multidimensional categorical data. The visualization lays out axes in a parallel way where each axis represents one categorical dimension. Within each axis, boxes represent the categories which are scaled according to the respective frequencies. Applied to Markov Models, the categorical dimensions correspond to the various cycles. Joint probabilities of categories from adjacent axes are shown as parallelograms

connecting the respective categories. The parallelograms can be interpreted as the number of patients transiting from one state to another. Depending on the purpose, the color of the parallelograms indicates the categories of a chosen cycle or could refer to additional attributes of the patients like age or sex. (see Figure 5)

State probability and survival curves merely show specific aggregates of the data while classic Markov trace visualizations with for example bubble diagrams do not visualize data in a sense that would facilitate a detection of proportions and trends. Applying Parallel Sets to analyze Markov models provides an interactive visualization technique where changing the reference Markov cycle is as easy as highlighting particular dimensions, thus enabling the exploration of the progress of patient cohorts with certain characteristics through the model. Model development always requires thorough analysis of its structure, behavior and results.

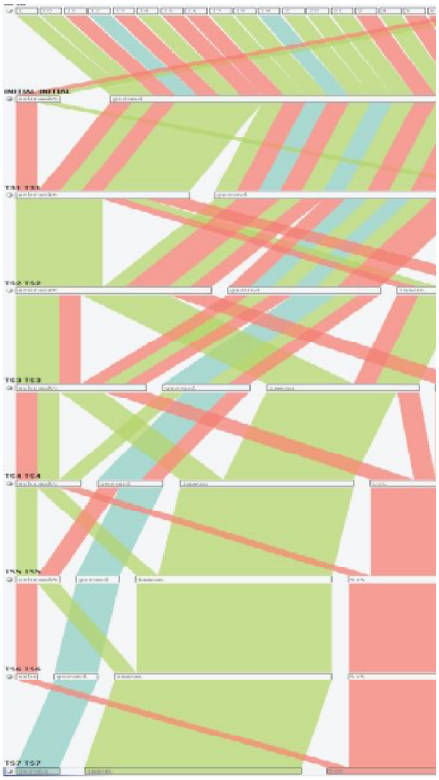

Figure 5: Parallel Sets enable an intuitive and efficient visualization technique for presentation purposes as well as exploratory analysis.

SUMMARY

The research project description presented in the paper shows how different expert domains can be joined to an overall approach in model based HTA of infectious diseases and vaccination strategy evaluation. As decision support has to become faster because of globalized interaction of people and therefore spreading of infectious diseases over borders and continents, a predefined work plan, parameter sources and modular reusable model parts are developed.

The theoretical work in the field of statistical methods, testing of adequate visualization methods and data quality assessment tools as well as a content management tool for the process guarantee that the boundaries regarding time span and quality can be observed.

The development of modern modeling methods and setting up an interdisciplinary process, dealing with the rising questions in HTA especially for infectious diseases and evaluation of vaccination strategy is realized. The description of the research project presented in the paper shows how different scientific domains can be joined to a joint overall approach in model based HTA. As decision support has to become faster, parameter sources and modular reusable model parts have to be developed in advance.

Using the developed knowledge and hierarchically structured framework an adequate system of decision support for model based HTA questions is realized. The closer look on Austrian data and healthcare system provides a fast implementation process for real world tasks.

ACKNOWLEDGEMENT

The Innovative Framework for Evidence based Decision making in Healthcare (IFEDH) research project is founded by the COIN – Cooperation and Networks program of the Austrian Research Promotion Agency (FFG), the national funding institution for applied research and development in Austria. The project is headed by dwh and lasts from October 2010 till September 2012.

REFERENCES

Zauner G., Popper N., Breitenecker F. Evaluation of Different Modeling Techniques for Simulation of Epidemics. *Proceedings of the 7th Congress on Modeling and Simulation.(2010) ISBN: 978-80-01-04589-3*

Miksch F., Popper N., Endel G., Schiller-Frühwirth I., Breitenecker F. *Herd Immunity as a Result in Dynamic Agent-based Epidemic Models. J. Wiley; Value in Health / Wiley-Blackwell, Vol. 13/ No. 7 (2010).*

Zauner G., Popper N., Breitenecker F., Endel G.: Multi Agent Simulation Techniques For Dynamic Simulation of Social Interactions and Spread of Diseases with Different Serotypes. *Public Health Decision Making - Program and Abstracts. U. Siebert, E. Fenwick, J. Pliskin (Ed.); Target Conferences, (2010).*

Taylor D., Kruzikas D., Pandya R., Iskandar R., Gilmore K., Weinstein M. Methods of Model Calibration: A Comparative Approach. *Value in Health - The Journal of the International Society for Pharmacoeconomics and Outcomes Research* 2007, vol. Volume 10, Number 3, p. A7.