Bridging the Gap between Experimental and Nonexperimental Neuroepidemiology, and Ultimately – between Neuroepidemiological Research and Practice: Round Table Discussion at the First International Congress on Clinical Neurology and Epidemiology

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Key Words
Education · Neurology · Epidemiology · Evidence-based medicine · Clinical knowledge · Perceptions · Collaboration

Abstract
A highlight of the congress was an interactive and inclusive discussion of the existing gaps between clinical neurology and epidemiology and the ways of bridging these gaps. Some perceptions, challenges and scientific issues between experimental and nonexperimental neuroepidemiology were brought to light. Recognizing that all study designs have advantages and disadvantages, panelists stressed that studies should aim to complement each other while answering important research- or practice-related questions. Advocated strategies included introducing more epidemiology into the medical school or residency curriculum, developing consistency in the reporting of epidemiological data to improving the strength and utility of the evidence, as well as nurturing collaborations that recognize the usefulness of both experimental and nonexperimental epidemiological studies. These strategies will in the end benefit clinical practice. Indeed, clinical knowledge improves with experience and critical scientific evidence that can change perceptions, yet, individualized disease management will probably always remain an art rather than an exact science. Nevertheless, strong epidemiological studies and collaborations can influence government and public health policies. Bridging the gap between neuroepidemiological research and practice – whether through improved communication, education or basic science – is clearly a pressing challenge that requires our concerted and sustained effort.

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Introduction

The First International Congress on Clinical Neurology and Epidemiology was held in Munich, Germany from 27 to 30 August 2009. There were 220 actively involved participants, representing 43 countries (fig. 1). On the second evening, the Neurology and Neuroepidemiology Summit session was held. In this ‘Round Table’, we sought to talk and listen to each other on what can be done to improve communication and interface between epidemiology and clinical practice and bridge the gap between experimental and nonexperimental neuroepidemiology. Bringing together neuroepidemiologists, practitioners, public health physicians and health care policy makers, the discussion centered on the challenges and approaches needed to bridge the gap not only between trialists and nonexperimental neuroepidemiologists but also between academicians and practicing physicians, thus facilitating the implementation of the most effective, evidence-based treatment, rehabilitation and preventative strategies of neurological disorders. Specifically, we asked:

1) Can epidemiology contribute to the practice of clinical neurology?
2) Why is there a lack of communication or links between clinical trialists and ‘pure’ epidemiologists?
3) Can randomized controlled trials (RCTs) be of help in addressing some of the issues in nonexperimental neuroepidemiological studies?
4) What are the limitations of evidence-based medicine (EBM)?
5) Can nonexperimental neuroepidemiological studies be of help in addressing some of the issues of treatment effects?
6) What are the alternatives? and lastly,
7) Where do we go from here?

Ultimately, practical solutions should share the common objective of reducing the burden of neurological disorders, through the influencing of decision-makers and improving public awareness, with well-conducted data-driven research, critical appraisal and collaboration.

Fig. 1. Distribution of the participants at the First International Congress on Clinical Neurology and Epidemiology (shaded/yellow areas represent participating countries).
Contributions to the Clinical Neurology Practice

The discussion opened on whether epidemiology can contribute to the practice of clinical neurology. Although neuroepidemiology has and continues to add to clinical knowledge in neurology, there appear to be barriers in acceptance or implementation. Some of these barriers come from our perceptions. Starting from the guiding principles of clinical neurology practice, Prof. Kurtzke reflected on the practice of clinical neurology and epidemiology. While the main difference between these worlds is simply that the former is primarily concerned with the care of an individual and the latter is interested in groups, this difference which is perceived to separate should, in reality, encourage the disciplines to find ways to complement each other’s knowledge.

The neurologist is concerned with anatomical localization, neurological examination, brain imaging and laboratory analyses, and differential diagnosis leading to conclusions for the next steps. It is neurologist’s responsibility to treat patients with competence, integrity, respect and compassion. This requires knowledge not only of the nervous system and its disorders but also the consideration of the age, sex, occupation, beliefs and home situation of the patient.

To the epidemiologist the same principles apply. Approaching the community with competence, integrity, respect and complete objectivity without preconceptions or bias, the epidemiologist seeks to define the characteristics common to a group for a specific purpose. This purpose can be to describe disease, investigate causes, assess its treatment, or measure its occurrence in time and place. If a neurologist wants to investigate a disease in groups, then he functions as an epidemiologist.

Epidemiology is the study of frequency, distribution and determinants of disease in human populations, and has often been called the basic science of clinical medicine. Frequency, distribution and determinants or risk factors are calculated from a population sample. To define a disease requires distinct groups or clusters, such as groups for cause and treatment, groups to describe its acute etiology, and so on. The fundamental charge of the epidemiologist is to ask focused questions to find out more about the disease, its treatment or its occurrence in time and place. As complete assessment of the population is rarely possible, especially in uncommon diseases, statistical inference and the concepts of external and internal validity apply [1].

All studies need to be critically appraised. Publication of negative studies should also be encouraged, as these also contribute to clinical and scientific knowledge of what not to look for or consider. Starting from case series and progressing along the line of evidence hierarchy to RCTs and meta-analyses, the source population always needs to be considered and since it is all clinical data (i.e. deriving from patients), the reasons behind the existing gap are quite curious.

One of the problems with the lack of dialogue or linkages arises from the fact that in most clinical trials, the conclusions and outcomes do not meet or match the population as a whole (i.e. the external validity of the study is very low). Thus, the community neurologist may believe that the work just does not apply in his/her context. However, trialists are not the only culprits who often fail to see outside the standard RCT box, and further education of the organizations that routinely and exclusively use RCTs as a means to an end is needed. The important comment was also made that while epidemiologists contribute through their focus on identification of commonalities within groups, clinically, practitioners are often most interested in the exceptions to these rules, and can thereby inform further epidemiological exploration.

Another way to bridge the gap worldwide would require the gap in health disparities between resource-rich and resource-poor countries or regions to also be considered and minimized. Instead of huge trials with costly drugs studied mostly in industrialized nations who can afford the current system, smaller focused trials that are feasible and cost contained for developing countries using drugs or interventions with moderate risk (e.g., aspirin) should be conducted for a wide variety of diseases instead. Prof. Roth well spoke earlier in the conference about the simpler interventions that are readily available, which we should be confirming in pragmatic trials and/or nonexperimental epidemiological studies. These more transferable studies to the community practice, i.e. those with high external validity, should help decrease the gap between the results of trials conducted only in high-resource specialist centers and the field neuroepidemiologists.
It is also possible that the gap arises from collecting the information. Prof. Beghi insists that we can improve the link between clinicians, trialists and neuroepidemiologists by improving the ways routine data are collected, citing the improvements with use of registries in countries with national healthcare systems. Arguably, there is a lot of information that is available or comes out in clinical practice – some is available as part of the public health system in some countries (e.g. Italy, Ireland, UK, Sweden together with the other Nordic countries); however, some is locked by private or managed care insurance companies (e.g. in the United States). Although time consuming, it would be useful to mine this huge amount of data. It is up to epidemiologists to compel our governments to see this priority. There are examples of registries in Italy that demonstrate how the information can be used to improve care (e.g. in amyotrophic lateral sclerosis). With increasing validity and continuous improvement in the routine data collection, this information can be extremely relevant when fed back to the clinician.

Prof. Li talked about a positive example from China on the extended collaboration of neurologists and epidemiologists. When the government became involved, giving funds of several million Chinese Yen, the studies were well received and the investigators, neurologists and epidemiologists, were able to promote changes in policies towards the rural areas. In China, more clinical neurologists reach a professional level through on-the-job training and there are already clinical epidemiologists of high level expertise. This environment makes positive collaborations possible.

Although there is agreement that positive examples of collaboration exist and there is a lot of available information, the next question is why do not epidemiologists in the field use data from other trials? The answer to that is much deeper than yet remarked. The decisions that are made in the field are much more complex. Vice versa, the implementation of research in the clinic is harder than one would expect in this climate of EBM and it is very difficult to change perceptions.

Furthermore, it seems in some areas that nothing advances without the epidemiologist. Neurologists must learn to read the study and understand how to implement and interpret the information on a case-by-case basis. On the other hand, many neurologists find the wonderful, clean data presented from clinical trials simple and easy to use. This is an issue in Japan. Prof. Nagata conceded that much more dialogue between clinical trialists and neuroepidemiologists is needed, because of differences in Caucasian and Japanese patients, and often the data can not be simply applied.

It is plausible that basic science can also bridge the gap, bringing new ties through research at the molecular or systems level. However, this needs to also be a two-way relationship, as sometimes basic science is uncritical in its acceptance of a model from epidemiological studies, which then fails to work. Indeed, there should be less ‘silos’ in research. It is entirely plausible that the epidemiological model developed from specific population-based studies needs basic science or systems biology approaches to complement the findings and explain more of the variability seen in the data.

Finally, Prof. Logroscino asked us to consider one other source of this gap. In the United States, perhaps the responsibility lies particularly in the separation of the schools (i.e. public health in one corner and medicine in another). In Europe, epidemiology is more integrated into the medical curriculum but often only in postgraduate training. These different approaches need to merge such that epidemiological methodology is taught in medical schools across the world. At the moment, approximately 45% of American medical schools have committed to having a course in epidemiology and/or EBM developed by an ad-hoc committee of the American Academy of Neurology within their residency programs in the near future. Arguably, this type of change in education is the critical component to ensure that the gap between neuroepidemiological research and clinical practice is narrowed in the future.

**Evidence-Based Management: Who Benefits?**

There is no question that EBM is needed in this era of budgetary constraints, especially as the costs and development of advanced therapeutics and interventions are spiraling. Ideally, EBM should guide clinicians for making the correct diagnosis or for use of the drug or intervention and provide some interpretation. Often when meta-analyses are performed, it is said that the interven-
tion is used to treat disease. It is more appropriate to say that the intervention is used to treat people. Prof. Korczyn suggested that this is a useful distinction to remember.

In EBM, the double-blind RCT is the gold standard. As most often is the case, RCTs are placebo-controlled, which makes ‘gold standard’ an expensive assumption, as RCTs do not always provide useful answers to clinicians in specific cases – meaning that the results of RCTs have sometimes low external validity. The main limitations of RCTs are that they are not always feasible due to the disease condition or ethical reasons and a placebo is not the ideal comparator. Unfortunately, very few so-called head-to-head studies are performed with the investigational treatment against the current ‘best available’ treatment (mainly because of the financial costs involved and the fact these studies are often industry-sponsored). For the most part, RCTs are often not easily extrapolated to the real world, as exclusion criteria can be too tight and studies are usually powered only to demonstrate benefit in the primary endpoint, not for overall safety or specific adverse events.

Furthermore, it is important to understand the sources of selection bias in RCTs. Of course, the study centers chosen are not random; the centers in many RCTs are where the doctors are trained for conducting trial procedures and are sometimes contract research organizations. These centers are aware of the trial requirements and are specialized, more than perhaps, the average community-based clinician. Furthermore, patient recruitment is often from failed previous studies and these patients may not represent the community in many ways, including their motivation to participate in a clinical trial.

Another consideration in the usefulness of RCTs should be the publication bias towards positive studies as well as information bias. Although this is changing slowly due to the intense legal scrutiny the pharmaceutical and medical device industry are experiencing, it does leave questions regarding the bias in earlier meta-analyses, done using the available, mostly positive, published studies.

In essence, pharmaceutical and device clinical trial data are accumulated primarily to convince regulatory authorities, not to guide clinicians. In addition, there may be a certain amount of ‘censoring’ in keeping with the company’s marketing messages. In neurology, data from industry-sponsored trials are often cherry-picked for publication; although the overall presentation might be balanced, the data chosen for publication appears to primarily support marketing messages and ultimately a promotional use for the article. There has been recent controversy on authorship issues, ranging from not only who actually writes the clinical trial reports, but for journal publication (i.e. what conflicts of interest are there and are they reported). Furthermore, there have been several cases where authors, whether opinion leaders or study investigators, have not seen all the raw data. Due to the proprietary, legal and perhaps even financial reasons of the trial industry sponsor, the author-investigator is often not allowed to run his/her own analyses, leaving much to be desired in terms of transparency. Thus, these publications should be taken with pinch of salt, as the main beneficiaries are the drug and device industries, and not necessarily clinical medicine and science.

Nevertheless, it is important to remember that EBM has been and still is a good instrument. In a very short time, RCTs have produced a lot of knowledge in many neurological aspects. There are RCT designs which can be used for answering epidemiological questions, and large pragmatic studies have been conducted that have made substantial contributions to the understanding of the underlying processes and the natural history of disease. The recommendations from ‘strong evidence’ RCTs, albeit selective in their patient population, have improved the clinical care of the standard patient, which on a normal curve probably accounts for up to 20% of patients.

Of course, most patients encountered in the neurological trial setting are atypical. It will not be possible or even meaningful to implement every single EBM recommendation for the majority of patients in the community practice, as most do not meet the inclusion criteria, have comorbidities or extended presentation, or are unable or unwilling to follow the strict protocols from such trials. The presence of comorbidities, for example, is one of the primary problems with aging of the general population. Future users of the drug previously tested in the RCT will probably be older and with more comorbidity compared to the healthier subjects who were enrolled in the previous RCT. Although the results might be statistically significant, as critical thinkers and clinicians, it is imperative
to consider the effect size and clinical relevance to the situation at hand, before implementing new evidence in clinical practice.

**Complementary and Pragmatic Studies**

In general, clinical trials provide evidence on whether treatments or other interventions result in improved outcomes in groups of individuals and are performed in such a way that random error is minimized and bias is controlled [2]. It is true that conducting a standard double-blind RCT on a neurological disorder is not always realistic, as often a basic assumption is violated (blinding, etc.). Another option is the randomized pragmatic trial.

The ‘large simple’ trial or pragmatic trial tests for effectiveness (‘does it work?’) rather than efficacy (‘can it work?’). The benefits of a pragmatic trial include having a broader, more representative study population, using treatment modalities and comparators that are closer to clinical practice, having an extended follow-up period, and more often than not, producing results of high external validity. The drawbacks are that there is often a possibility of an unbalanced distribution of prognostic factors, negative results may hide a subgroup that would benefit, and internal validity may be imperfect. They also do not explicitly answer the question of primary interest to practitioners that is ‘With whom does it work best?’

Of course, study designs without randomization or intervention are available to answer different questions. Cohort studies, observational studies and surveys are some examples. In general, the main advantage of a cohort study is that it allows one to study multiple exposures and multiple outcomes in a single cohort. Even rare exposures can be studied, for the index group can be selected on this exposure; the combined effect of multiple exposures on disease risk can be determined. Cohort studies are also used by researchers to generate hypotheses to be trialed in a RCT.

The main disadvantage of a cohort study is that it cannot be used to reliably establish causal effects. As the exposure is not allocated randomly, there is always a possibility that the association found may be explained by other factors or confounders, i.e. variables that differ between exposed and nonexposed subjects but also have an association with the outcome studied. If these other variables could be measured, adjustments can be made for them in the analysis. However, these variables are frequently unmeasured, measured imprecisely or unknown. Moreover, cohort studies are prone to selection bias or referral bias. The index group has been formed not only by the exposure, but was already more likely to have the disease of interest at the beginning of the study. A similar bias can be introduced at the end of the study period. Sometimes disease status data are missing or cannot be measured because volunteers are ‘lost to follow-up’ – they have no complaints and/or are too busy or more importantly, they are too ill. This kind of selection bias can only be prevented by maintaining high rates of participation and follow-up.

Another important way of looking at the treatment effects over time in a population is through surveillance studies or surveys. One such example is the Oxford Vascular Study [3], which found that control of risk factors on the community level positively influenced incidence of stroke. Observational studies have advantages similar to post-marketing surveillance studies, where the study population is close to clinical practice over a prolonged period of observation. Even if the study is done prospectively, the pre-defined prognostic indicators can trace rare and chronic adverse events, and reaches the limits of external validity.

Therefore, one can complement RCTs with non-experimental studies. With a homogeneous inception cohort, well-defined validated diagnostic criteria (certain of diagnosis), use of matched controls (not placebo), blind assessors of treatment efficacy and safety, use of hard endpoints (less judgments on outcomes), predefined validated check lists of common adverse events – such studies will be robust and should have both good internal and external validity, if designed carefully, analyzed correctly and reported clearly.

In order for clinicians with no epidemiological training to pay greater attention to nonexperimental studies in neurological fields, neuroepidemiologists need to educate and set examples for highly readable and informative publications that can be used to combat negative opinions and perceptions. Particularly in those situations where RCTs are simply not possible to carry out, due to ethical constraints or lack of a realistic control popula-
tion (e.g. in neurorehabilitation), guidelines on how best to present neuro-epidemiological studies and meta-analyses of such studies that take into account all the evidence, including from nonexperimental epidemiological studies, are sorely needed.

Lastly, it is important to consider that by definition, meta-analyses can only include the published or otherwise available data and most focus only on the predefined primary endpoint. According to Dr. Bennett, it should be theoretically possible to combine data from groups using slightly different definitions of a similar secondary endpoint (such as cognitive function) in order to obtain summary effect sizes, as long as the pooled secondary endpoints are measuring similar phenomena (e.g. cognitive function measured by Mini Mental State Examination or telephone Interview of Cognitive Status). Meta-analyses of secondary endpoints in various types of trials can be useful if handled appropriately.

**Crossing the Bridge**

Often, it is unclear how to interpret RCTs, particularly whether the results can impact the general population. Only a small fraction of the available medical interventions, diagnostic and screening tools, surgical techniques and practice-related assessments are actually supported by RCTs. Monitoring changes in outcomes longer-term, similar to post-marketing surveillance studies can be of enormous benefit; this is one of the contributions of non-experimental epidemiological studies to treatment effectiveness for decision-making. Medicine still remains an art, as it is often the doctor driven to summarize the evidence, not only from RCTs but all the available evidence. The frustrations experienced in this process need to be minimized and the communication avenues improved. Where good observational studies are available and can contribute to clinical knowledge, they need to be well highlighted; in these cases, publication guidelines such as the STROBE [4] are extremely useful and could be extended for use in neuroepidemiology.

In case series and small observational studies, it would be ideal to track and identify characteristics of the source population; this valuable background information puts the outcome in context. However, by definition, collecting such information is almost impossible or unreliable and in practice unrealistic. It can be argued that only when a clinic is the sole provider of therapy for that specific disease in that area is this information useful, which is more often the case with chronic disease. A bigger challenge that affects epidemiological data is the people who go to seek medical attention are only a small proportion with disease and are usually different from those who do not seek medical attention. In order to really understand the source population, the full phenotype of disease would need to be known, which is time consuming, requiring considerable funding to the point of impracticality, especially for uncommon diseases.

Clearly, this is a central issue considering the finite and limited resources and it will not be resolved anytime soon. However, from an epidemiologist’s point of view, the current ad hoc way of reporting information makes it very difficult to use data, because one cannot call it good evidence simply because there is no denominator reported in the study. The careful epidemiologist, trying to integrate this new data without some sense of the source population, has no idea who the patients are or from what kind of healthcare context they may come. A high level of communication and transparency is needed to fill the gap in the knowledge. This would enable integration of data from different sources with greater confidence and thus improve the generalizability of nonexperimental epidemiological work. By insisting on these requirements at a high level, it begins to change the way the clinicians think about the results and re-enforces the value of nonexperimental epidemiological studies.

Perhaps it is the scale of the challenge that makes it so daunting; within one institution, bridging the gap is feasible in the short term. But in the long term on a country-wide, or even global scale, the improvement in education is needed first, which stresses that epidemiology is really not difficult and is a basic clinical science. Close collaboration with ideally ‘open source’ data should be more commonplace, albeit privacy issues and potential loss of information may come into play. The scale of collaboration does not need to be very complicated. Neurologists and epidemiologists are both well-trained in a rational way of thinking, so this alone should lead to designing statistically robust data analyses of practical relevance.

However, in Prof. Beghi’s experience, trying to involve clinicians in epidemiological studies is not...
always positive. Initially enthusiastic in his department, he noted that unless clinicians are already interested in tackling the problem on a population-wide basis, getting a registry together can be difficult. As the general neurologist typically sees a patient with a specific neurological disorder only a few times a year, they are often not interested in counting. Prof. Beghi insisted it is not a matter of wrong or right, just that the interest of each side needs to be considered carefully in order to be more realistic about the success rate of this particular strategy.

An exemplary program from the Mayo Clinic (Rochester, Minn., USA) illustrates how bridging the gap could work in a clinical setting. Associate Prof. Brown talked about his experience with Mayo Clinic’s Rochester Epidemiology Project [5] and its use in population-based outcome survey research and community-based practical behavioral trials [for further information see 6]. The Mayo Clinic is a large multi-specialty practice which provides a unique opportunity to develop longitudinal standardized data sets, as it is effectively the only neurosurgical, cerebrovascular, and rehabilitation practice that serves the population of Rochester and Olmsted County, Minnesota. Recognizing that the patient’s long-term needs after brain injury are primarily rehabilitative [7], brain rehabilitation clinicians have developed a coordinating role for medical care across disciplines and departments along the continuum of recovery. Over the years, the Mayo Clinic has developed a service line approach to the clinical management of acquired brain-related neurological impairment, treating it as a chronic disease rather than aligning care by the diagnoses that make up the service line (stroke, status-post craniotomy, traumatic brain injury). Individuals with service line diagnoses are identified when they first present for care, with standardized administrative and clinical information gathered longitudinally, including outcome and satisfaction data. These data are used to inform clinicians providing care, constituting a practice-based evidence approach to the continuous improvement of a disease management strategy for chronic brain-related neurological impairment. Because of its unique position in the community and region, this approach at Mayo Clinic offers the potential to merge prospective population-based clinical care and outcome data with neuroepidemiological research.

Patient-specific data of this kind also allows care to be customized based on patient need and unique clinical characteristics. However, the use of data for research requires consent and many important issues related to data privacy are emerging as medical databases develop, particularly as genomics becomes integrated into routine clinical practice and tissue samples are banked.

This example is truly a localized and individualized approach, which addresses most issues of bridging the gap – the merging of epidemiologists who manage populations and clinicians who manage individuals – however, it may be difficult to implement or translate these findings to clinicians everywhere. It is important to remember that all solutions eventually are contextual (i.e. dependent on the local healthcare environment). Findings should be confirmed in various geographic and care settings to determine the best solution for a given region. While collaborations and infrastructure need to be specific to a community, we still can learn from each other’s experiences. Individualized care implies that the treating physician makes management decisions based on patient need and thus, disease management will always be a creative process.

**Conclusions**

There is nearly no aspect of the healthcare system that would not profit from epidemiological studies. The existing gap between experimental and nonexperimental neuroepidemiologists is due to a multitude of factors, including the perceived differences between the goals of neurologists and epidemiologists, the varied complexity and source of studies and the extent to which they are digested in scientific communication. The main advantages and disadvantages of both experimental and nonexperimental studies were discussed; it was noted that studies should and do often complement each other and positive collaboration can be made. Whereas RCTs are primarily used by drug companies for regulatory approval and can have limited external validity in the community setting, post-marketing surveillance (performed independently from the pharmaceutical companies), pragmatic trials and well-designed observational studies can help bridge the gap between the ‘ideal’ and real patient cohorts.
Perhaps it truly is a trade-off; a balance must be struck between the advantages and disadvantages of the different study types and objectives when it comes to critical appraisal of the evidence and in the context of clinical experiences in each country. Concerted actions between neurologists and epidemiologists are needed to influence governmental or public health decision-makers, as well as improve public awareness, in order to reduce the burden of neurological disorders in each country or community.

The Round Table was successful in creating a platform for such thought-provoking discussion. All participants appreciated the need to bridge the gap between research and clinical practice and between practicing and academic neurologists and epidemiologists. Clearly, some of the strategies are already in progress; our students and their future patients will inherit the benefits of our incremental improvements, particularly the increasing frequency of collaborations and the opening of communication avenues we make today. Indeed, the more we talk about it, the more we can come up with ideas and discuss strategies to go forward. We hope to see you at our next (second) 2011 International Congress of Neurology and Epidemiology in Seville, Spain in March for updates and further lively discussion.

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