

## Building Bridges between Healthcare and Public Health From Efficacy Trials in Patients to Those Effective in Populations

*Crear puentes entre la atención médica y la salud pública  
De los ensayos de eficacia en pacientes a los de efectividad en poblaciones*

*“Working together, clinical medicine and public health may guarantee that persons lead active and productive lives much longer than it was ever thought possible.”*

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### INTRODUCTION

Despite the increase in obesity and physical inactivity, premature death and disability due to non-communicable diseases (NCD) substantially decreased both in the United States as in other high income countries during the period 1990-2010. However, in low income countries, in the same 20-year period, the increase in death and disability due to NCD was 300% higher than the decrease in the load of infectious diseases. Moreover, also in mid-low income countries, the growth of NCD overcame by 33% the reduction in communicable diseases during the same period. (2)

Therefore, today NCD are the main cause of death and disability in low income and mid-low income countries, where they have killed almost 8 million persons below 60 years in 2013, at a living and working productive age. (3)

The recent improvement of life expectation in developing countries cannot explain why so many people in these countries are acquiring NCD at a much younger age and with worse outcomes than in richer countries. Although obesity, ultra-processed food consumption, physical inactivity and tobacco are fast increasing, their growth, except for tobacco, is far below than in most high-income countries. It can then be concluded that in emerging countries premature death and disability for NCD is growing associated to poverty, same as in the poor sectors of the richest countries.

The dramatic changes in urbanization, global companies and consumer markets are developing at a much faster rate in still poor countries than they did in developed countries in the past, associated to the inability of developing country governments to establish health systems and the necessary regulatory mechanisms to avoid the exponential epidemics of NCD.

If these trends are preserved or accelerated, the toll of lives for NCD on the working-age population

will increase in these countries.

Therefore, it is now essential for us, the health professionals and workers, to build a bridge between medical assistance and public health measures, in order to change this devastating trend for our countries in the next decades.

### THE DEVELOPMENT OF CONTROLLED RESEARCH IN PATIENTS

For over the past five years epidemiological science has had a predominant position in the development of preventive medicine for non-communicable chronic diseases, since Austin Bradford Hill and Richard Doll made a major contribution with the breakdown in the knowledge of the cancerous effect of tobacco in 1950.

They taught a posterior generation of epidemiologists to think quantitatively and introduce a new research methodology with the creation of new designs (controlled clinical trials, case-control designs and large population registries) and the growing influence of medical statistics, following pioneering studies by Karl Pearson, teacher of Bradford Hill, who founded the Department of Applied Statistics at London University. (4)

At the beginning of the seventies, with the appointment of Doll as royal professor at Radcliffe Infirmary hospital, Richard Peto was incorporated. He already had the firm belief that the existing methodology for clinical trials was grossly inadequate to show unequivocal results, because trials were very complicated, performed in few university centers and with a ridiculous number of patients. He thought that knowing the moderate effect of a decrease in mortality (20% to 30%) concerning prevalent chronic diseases as cancer and cardiovascular disease could have a great clinical impact saving thousands or hundreds of thousands of lives. To achieve this end it was necessary to perform large randomized clinical trials, sufficiently simple to include not hundreds but thousands of patients.

In 1975, Peto founded the Clinical Trial Service Unit in Oxford and in 1976 Salim Yusuf went from India to Oxford to work with Peter Sleight, professor of Cardiology, to investigate whether beta-blockers could decrease the complications of acute myocardial infarction. He consulted Richard Peto to perform a large dimension study, 10 to 20 times larger than

what was commonly thought at the time. At the beginning of the eighties, the ISIS-1 (International Study of Infarct Survival) trial was developed. It was a great challenge carried out in 245 Coronary Care Units of different countries, including more than 16,000 patients. The study finished with the incorporation of a 26-year old research doctor, Rory Collins who, despite the ISIS-1 results were negative, planned the ambitious and bold ISIS-2 trial, considered one of the most important steps in acute myocardial infarction (AMI) management. The idea of the project started with a meta-analysis of the Oxford team on all the small previously negative studies of a drug that dissolved the clot, streptokinase, showing as a whole, 20% reduction in the number of deaths, and another meta-analysis of aspirin in stroke and heart attacks with the concomitant reduction of death. The trial decided in a joint meeting in Peter Sleight's home, a fact that was essential as he was a cardiologist trainer of cardiologists, to perform a study that some cardiologists considered was planned by Martians.

A total of 417 hospitals and 16 countries took part of the ISIS-2 randomized, stratified trial with streptokinase and aspirin, consisting of four treatment groups: streptokinase or aspirin alone, both drugs, or none, in patients with suspected AMI. In the meantime, Lancet publishes in 1986 the Italian randomized, open-label streptokinase and control study with 11,806 patients, from the Italian Group per lo Studio della Streptocinasi nell' Infarto Miocardico (GISSI) showing a significant reduction of AMI mortality. (5) This facilitated the final ISIS-2 recruitment which after 3 years ended with the news that both streptokinase and aspirin moderately reduced mortality saving hundreds of thousands of lives worldwide.

We have taken a major step, but we must now move to a generalization of research on the usual clinical practice and on population prevention measures.

A known clinical trial researcher in cardiology has broadened his perspective towards a global epidemiological investigation. Salim Yusuf says: "In INTERHEART and subsequent studies, such as the Prospective Urban Rural Epidemiologic (PURE) study, we explored why people have risk factors, the causes of causes. This means looking for the social determinants of health and environmental factors and their influence on health behaviors, risk factors and diseases." (6)

Looking for the causes of causes is also the turn imprinted in the investigations of Giani Tognoni from the GISSI studies and the Mario Negri Institute and Valentín Fuster from the Mount Sinai Hospital.

#### **EFFECT OF SOCIAL HEALTH DETERMINANTS**

In turn, the director of Lancet, Richard Horton, with a selected core of epidemiologists has recently emitted a declaration titled: "From public to planetary health: a manifest".

This manifest to transform public health calls

upon a social movement to support the collective public health action at every level of society –personal, community, national, regional, global and planetary.

"Planetary health is an attitude towards life and a life philosophy. It focuses on persons, not on diseases, and equity, not the creation of unfair societies. We seek to minimize the health differences depending on wealth, education, gender and place.

The damages we continue to inflict on our planetary systems are a threat for our existence as species... We have created an unfair economic world system favoring a reduced elite of rich persons, over a vast number that have so little". (7)

An urgent transformation of our values and practices is required based on the acknowledgement of our interdependence and the interconnection of the risks we face.

"... We need a new vision of cooperative and democratic action at all the society levels and a new principle of welfare in the planet for every person on Earth – a principle that states we must preserve, maintain and make resistant all the planetary systems and humans upon which health depends, giving priority to everybody's welfare.

...The voice of public health and medicine as the independent consciousness of the planet's health must have an essential role to achieve this vision. Together with the power of communities, we can face the ingrained interests and forces which endanger our future. A powerful social movement based on the collective action at all the society levels will provide planetary health and, at the same time, will support a sustainable human development."(7)

It is outrageous and disgraceful that 60% of deaths and 35% of births in the world are not recorded in registries, (8) and that in the remaining 40% registered deaths, one out of four is ascribed to vague or ill-defined causes. (9)

The WHO Commission on social determinants of health declares: "... the structural determinants and daily life conditions constitute the social determinants of health causing much of the health inequity within and between countries..."

Society has traditionally looked at the health sector to take care of its health and disease concerns. Of course, the bad distribution of healthcare – for example, not providing care to those that most need it- is one of the social determinants of health. But much of the high load of disease leading to a terrifying premature loss of lives stems from the immediate and structural conditions in which people are born, grow, live, work and become old." (10)

The life expectancy of a person who was born or lives in Japan or Sweden in over 80 years, in Argentina 76 years, in Brazil 72, and in India 63 years. In several African countries it is below 50 years.

"Inside countries, the differences in life opportunities are also large."

For example, in Tottenham, life expectancy is 71

years, 13 years less than in the rest of London and 18 years less than in Kensington-Chelsea. (10)

This phenomenon has also been shown in Argentina, where infant mortality is 2.2 times higher in the Southern compared with the Northern communes of the city of Buenos Aires, associated to a Southern family income which is half that found in Northern families. In addition, the mortality rate in persons <75 years of age is growing in the successive socio-economic quintiles of deprivation and this difference increased from 2000 to 2011. (11)

### **BUILDING BRIDGES BETWEEN MEDICAL PRACTITIONERS AND SANITARY PHYSICIANS**

Bridges should be built between healthcare and public health professionals. Although they have different perspectives, these are not contradictory, but potentially and necessarily complementary.

While everybody acknowledges –in the first place the patient- that the medical practitioner is necessary, the emphasis placed in the structure of brief meetings is not sufficient. Patients are treated as isolated individuals, not as members of a community, whose characteristics may affect their health.

Although visions and approaches seem very different because they have different perspectives, they need to complement “...how and when the community and public health effort must supplement individual medical care, or conversely, how medical care may help in the difficult public problems.” (12)

The efforts to simultaneously improve both personal as population health are hindered by the absence of communication and coordination, with partial and disconnected data and registries.

Both the professionals devoted to individual healthcare as those dedicated to public health should demand in each district the cumulative data of all the health providers and clinicians, both public and private, to obtain the identification of the populations and districts at greater need, and thus understand the intervening local factors.

In this way, managing the main public health results, such as life expectancy, chronic disease load and many others with a visual map (GIS –Geographic Information Systems) is a useful tool at the national level as well as at the level of each community, region or district.

One of the problems resides in how we understand “risk”. As doctors, we are used to the Relative Risk (RR), the times a factor decreases or increases the risk of the patient we are treating, and we mistakenly think that this is mechanically transferred to the population. However, to know how this risk factor impacts in the population we should calculate the Population Attributable Risk (PAR), which could be defined as the percentage of cases of a certain disease that can be avoided in the population if exposure to the study risk factor is eliminated. Let us consider as paradigmatic example the association between tobacco

and lung cancer; the RR of cancer increases 20-fold in smokers. However, to calculate PAR we must also know the prevalence of smokers in the Argentine population, which would approximately be 26%. Applying this prevalence and RR we can easily calculate PAR of tobacco for lung cancer (Figure 1)

This means, if the Argentine population did not smoke, the risk of lung cancer would decrease by 83%, immeasurably higher than any dubious screening method for early disease detection and patient operation.

But to demonstrate that the individual RR is not automatically transferred to PAR, we will pose the situation of patients with the genetic BRCA1 variant, which confers a 44-fold higher RR of breast cancer than in those who do not have it. We could call it the A J (Angelina Jolie) case; as her, many persons would request the State the possibility of detecting this variant in the general population to prevent the incidence of cancer.

However, the prevalence of this genetic variant in the population is 0.0007 (0.07‰), so that applying the above formula the result would be 2.9%. Breast cancer would thus decrease this minimum percentage if all the persons carrying BRCA1 in the populations were detected. It is evident that it is less costly and equally effective to perform the genetic test only in those persons having a young first degree relative with breast cancer.

In turn, the relationship of tobacco with ischemic heart disease is weak in the individual patient; his RR increases only 1.6-fold, but as the prevalence of smokers is 0.26, the resulting PAR is 13.5% and its reduction has great relevance in the population. (13)

### **SOME NEW WAYS OF PERFORMING OBSERVATIONS AND CONTROLLED POPULATION TRIALS**

#### **Samples representing the real population and sentinel systems**

Since according to the “Impact” program, the decrease in the number of deaths for coronary artery disease in the United States in the 20-year period extending from 1980 to 2000 was almost equally due to drug treatment, interventional procedures and surgery (47%) in patients with overt disease, and to risk factors which decreased in society (44%) (the model did not explain the remaining 9% of deaths), it is necessary to design researches covering both approaches, the treatment of the individual patient and the risk factor decrease in the population. (14)

$$\text{PAR} = \frac{\text{Prev. (RR-1)}}{\text{Prev. (RR-1)+1}} = \frac{0.26 (20-1)}{0.26 (20-1)+1} = 83.1\%$$

**Fig. 1.** Population attributable risk (PAR) calculation for lung cancer. Prev: Prevalence. RR: Relative risk.

In these situations it is necessary to design complex samples so that the persons included represent the population we wish to study, using cluster, stratified, multistage sampling (15), as usually employed in United States NAHNES (National Health and Nutrition Examination Survey) surveys. (16)

Hypertension is the sole condition that annually kills more people than tobacco, more than 9 million per year; however, only around 1 out of 7 persons in the world has controlled hypertension.

We need population sampling to identify whether jointly applied programs both at the individual level (with standardized simplified protocols, available drugs administered to all and the task assigned to nurses or easily accessible non-medical staff) as at the population level with low sodium intake, are successful.

In the United Kingdom, the voluntary negotiation with the industry decreased sodium intake by 15% (1.4 g/day) between 2003 and 2011. A substantial reduction in blood pressure (3.0/1.4 mmHg) was achieved in the overall population and 2.7/1.1 mmHg in the persons without anti-hypertensive treatment, with a concomitant 42% reduction in death due to stroke and 40% reduction of cardiac death. It is estimated that 25% to 33% mortality reduction could be attributed to decreased salt intake. (17)

A "Sentinel System" can also be developed, as in the case of the FDA, to examine in real time the information of systems that use the electronic clinical history to monitor the safety of already proven medical products. It allows answering specific questions about medical products, as the myocardial infarct rate among patients using oral hypoglycemic drugs. The initial Mini-Sentinel system ensures the privacy of data as it uses a distributed data and analysis system, collecting anonymous data through specific programs run at each center, that remains the owner of the original data. (18)

### The social network study

The introduction of public health interventions does not reach all individuals simultaneously because social relationships in the real world are not indifferent, and relationships are established in family, neighbor, working, affinity, friendship, and other networks.

The experience often propagates mouth-to-mouth throughout the population.

It should not be assumed that the diffusion of new health knowledge or protective conducts only requires a cognitive acknowledgement –that the Facebook or LinkedIn Internet message can deliver- without face-to-face physical assistance and training, "getting down to it".

Let us consider the example of the interconnected social network of the Framingham study (Figure 2). The propagation of cigarette was repeatedly examined in 12,067 persons during 32 years. The network was represented by clusters of smokers and non-smokers and this grouping was extended up to the 3rd degree

of separation.

The person quitted smoking in 67% of cases if the spouse also abandoned smoking, in 25% of cases if a sibling quitted the habit, in 36% if a friend did so and in 34% in the case of a workmate. These effects were not seen among neighbors of the same geographical area.

It seems relevant that socially related groups previously abandon this habit in order to quit smoking, as if there were a social agreement. (19)

The person-to-person diffusion of obesity and alcohol was also explored in the same interconnected social network of 12,067 participants of the Framingham study between 1971 and 2003.

A person became obese in 57% of cases if a friend became obese, in 40% in the case of a sibling, and in 37% in the case of the spouse. This mimicking did not occur among geographical neighbors. It should be emphasized that persons of the same sex had greater influence in obesity. Moreover, it is relevant that obesity seems to propagate by means of close social relationships. (20)

When someone changes to excessive alcohol consumption it affects others. The influence in a 1st degree relationship is 50%, in a 2nd degree relationship 36% and in a 3rd degree relationship 15% (friend of a friend of a friend).

These findings suggest the significant role a social network plays in the inducement to consume alcohol. (21)

Also people connected with many happy people up to a third degree of separation (friend of a friend of a friend) and who are central in the networks will be probably happy in the future. Longitudinal statistical models suggest that extra happiness results from the dissemination of happiness and not from the tendency of people to associate with similar individuals.

Happiness of people depends on the happiness of others with whom they are connected. Happiness, same as health, should be seen as a collective phenomenon. (22)



Friendship-based social network. Persons A and B both have 4 friends. It is more probable that the 4 friends of A know each other, that there is a bond among them. However, none of the friends of B know each other. Notice that C is more central than D. [modified from (24)]

**Fig. 2.** Interconnected social link [modified from (24)]



### The use of social networks in public practice

There is a first study comparing strategies focused on networks to promote the diffusion of innovation in social networks face-to-face with the real world. In a rural area of Honduras, with a population of 5,773 villagers, 32 villages (clusters) were assigned to one, both or none of 2 interventions (chlorine to purify water or multivitamin tablets).

Interventions were introduced to 5% of villagers, using the following design: 1) random selection, 2) the most connected persons and 3) the friends of those randomly selected at initiation.

The products were delivered in only one day to the selected participants, who were instructed on their use and taught about the interventions. They were handed out 4 vouchers to be used by others to withdraw the products. Then, each person who received one of the 4 vouchers also went to withdraw the products (second wave, cascade effect).

Judging from the recovery of vouchers, asking the friends of persons in a random sample of villagers to distribute the vouchers for multivitamin vials led to greater diffusion in these villages than asking better connected persons, or simply the random sample persons, to distribute the vouchers.

A total of 74.3% of vouchers were recovered in the villages selected to nominate friends, significantly different ( $p < 0.01$ ) from the 66.2% recovery in those with random selection and 61.9% in the ones where the most connected persons were chosen.

This study demonstrates that focusing in the more connected persons does not provide extra benefit in health interventions. Conversely, the technique that selects people by a friendship relationship produces a larger cascade of product adoption and health knowledge.

Focusing on the friends of a random sample is clearly simpler and cheaper, as there no need to know the complete previous social network "map" to look for those who are more connected. (23)

In low and medium income countries (LMIC), natural social networks may be essential for health results, building, for example, cascade effects among participants who are not target of the initial intervention, and improving their efficiency.

A systematic review identified 17 articles from 10 studies of sociocentric networks examining the health problems in LMIC. Nineteen articles from 10 studies were also selected on welfare development topics.

Human health and welfare are connected by dynamic social relationships, which are especially important when people depend, directly or indirectly, on the connections that support them. (24)

### Improving risk conducts with automatic messages to mobile phones

A first study randomly assigned a messenger program to mobile phones with a semi-personalized automatic strategy focused on simultaneously changing various

lifestyle risk factors, or on standard care. It included 710 patients with proven coronary artery disease from a tertiary hospital in Sidney, Australia. Patients in the intervention group ( $n = 352$ ) only received 4 text messages per week during 6 months, without personal interaction.

At 6 months, a significant decrease was found for LDL-cholesterol ( $-5$  mg/dL,  $p = 0.04$ ), systolic blood pressure ( $-7.6$  mmHg,  $p < 0.001$ ), and BMI ( $-1.3$  U,  $p < 0.001$ ), while physical activity increased 293 MET minutes per week and the number of smokers significantly decreased (RR 0.6,  $p < 0.001$ ).

The messages for each participant were selected from a message base according to baseline characteristics (e.g, if he/she smoked) and sent through an automatic, not interactive, messenger system.

Messages were sent with the preferred participant name and provided advice, motivation and information to improve the diet, increase physical activity and encourage smoking cessation.

We report some of the messages sent:

Smoking (Name) *"try to identify the trigger that makes you want to smoke a cigarette and plan to avoid it"*.

Diet: *"Do you know that 90% of people do not eat the daily recommended amount of vegetables (5 servings per day?"*

Physical activity: *"Hello (Name) walking is cheap. It can be done anywhere. All you need is comfortable shoes and clothes"*.

General cardiovascular information: *"Studies show that stress, anxiety and loneliness may increase the risk of cardiovascular disease. Please, call a health-care professional if you need help"*. (25)

### CONCLUSION

As Thomas Frieden declares in the legend: "Working together clinical medicine and public health may guarantee that persons lead active and productive lives much longer than it was ever thought possible". (26)

If we persist in this epidemiological framework of new epidemics produced by socio-economic structures, future clinical medicine discoveries would only increase healthcare costs without substantial improvements in health outcomes. But if alternatively we develop new healthcare models and technologies, we may markedly increase a healthy life expectancy.

At the same time, the field of population health should be actively observant to adapt to new changing risk factors and to encourage public health actions which are the core to promote healthy lives. And in addition to the initial success of infectious disease, tobacco and alcohol campaigns, which should be reinforced and extended to be completely successful, the radio of action to control new epidemics due to environmental risk should be expanded, reducing damages produced by changes in the environment, increasing physical activity and above all, substantially

improving human nutrition technologies.

“Working together more closely, clinical medicine and public health may mutually help to maximally improve health –and emphasize the responsibility society has to encourage healthy and consistent environments, as well as high quality care.” (26)

It is our responsibility, as physicians in the care of our patients, to promote them.

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