Vol 2 (2) 2021

EFI Bulletin

Bulletin of Epidemiology Foundation of India

In this issue

President's Corner

Evidence-based medicine (EBM) is ranked seventh among the 15 most important milestones that shaped modern medicine. These milestones include the introduction of antibiotics, immunization, sanitation, and radiology. The EBM science was started in 1981 when a group of Clinical Epidemiologists in Canada, advised physicians "how to appraise" themselves with medical literature in their clinical practice. EBM is defined as Integration of the Best Research Evidence with Clinical Expertise and Patient Values. Recently, the grades of Quality of Evidence have been categorized that are as follows;

Level I: Large randomized controlled trials (clear results, low risk of error)

Level II: Small randomized controlled trials (uncertain results, moderate to high risk of error)

Level III: Non-randomized trials, contemporaneous controls

Level IV: Non-randomized trials, historical controls

Level V: Case series, no control

Globally in last 2 years the term 'Evidence' has been utilized extensively by all health planners, administrators, programme implementers and the scientists, to advocate an approach for COVID Management including treatment, prevention, recommendations of new strategies. Hundreds of publications have been made, some of these have been withdrawn after their publications even in reputed international journals or at times by the authors themselves as there was inadequate evidence to support their published findings. These developments reinforce the utility of field of epidemiology which helps in generating evidence in science.

It has been observed that at times, scientists undertake 1or 2 cross-sectional /case-control/pilot studies and start advocating that their findings as ultimate answer to a health issue. This happens more frequently when they belong to Institute of "National Importance" and they do not update themselves with the current developments in the scientific literature. They also teach their students same perspective. Majority of these teachers, at times, are not aware about the "Grades of Evidence" in Medicine.

Presently, the food industry is well aware of the power of science-driven headlines and has invested in meta-analyses. In the process, nutritional science at times is adversely affected. Meta-analyses in nutrition are of tremendous importance to the scientists and public. This is highest level of scientific evidence and can influence policies on diet and health. When the results of meta-analyses are the product of faulty methods used in meta-analysis the evidence can be misleading and can also be exploited by economic and commercial interests seeking to counteract true scientific findings about commercial products. Presently, Nutritional science has special challenges for meta-analyses. In clinical

trials, nutrition interventions vary from one study to the next in many methodological details, weakening the argument for combining their results. Combining results is very time consuming and difficult as this may require contacting the original investigators for participant-level data, original data of the subjects studied, which may have been produced using dissimilar dietary assessment techniques and methods.

The effects of any given dietary exposure depend on what that exposure is compared against. A meta-analysis in 2017, evaluated associations between red-meat intake and blood lipid concentrations. Of the 39 trials that were included in the analysis on low-density lipoprotein (LDL) cholesterol, 34 compared red-meat with other meats, revealing little apparent relationship with LDL cholesterol. The remaining 5 studies compared red-meat to plant-based foods, most of which found non-significantly increased LDL cholesterol after red-meat consumption. However, the investigators combined the results of all these studies, concluding that red meat "does not negatively influence cardiovascular disease risk factors.

Scientists need to be careful because meta-analyses, particularly involving diet influences health policies, carry considerable weight in the media and in public perception and have the potential to do harm. The peer-review process for scientific journals must go beyond ensuring that standard meta-analytic procedures have been followed. This could include (1) requiring review by editors with expertise in meta-analysis and in the subject matter at hand,(2) requiring authors to confirm with the authors of the original reports that their data were appropriately represented, to the extent possible, (3) requiring authors to share their summary data and methodological details to allow others to reproduce the analysis, and (4) prioritizing meta-analyses derived by pooling original primary data over those using published summary data.

Potential "conflicts of interest" should be carefully scrutinized for meta-analyses and the studies they include. This process should be facilitated by a standardized, permanent financial disclosure registry. These steps may not eliminate controversial findings from meta-analyses of nutritional research or of other topics but may give them a more solid foundation.

This message has been adapted from following publications.

1. A brief history of evidence-based medicine (EBM) and the contributions of Dr David Sackett. 2015 Nov;35(8):NP261-3. doi: 10.1093/asj/sjv130. Epub 2015 Jul 9.
2. The Misuse of Meta-analysis in Nutrition Research 2017 American Medical Association. George Washington.

Umesh Kapil

From the Editor

Probably we all had an optimistic view that the post-pandemic era starting early 2021 would bring solace and relief worldwide. But certain predictions for a second wave of COVID-19 had come true. During the recent past with a sudden peak observed in April-May we have terribly lost several of our most active colleagues of eminence including some established practitioners in public health. The concerns expressed by many proclaimed medical experts and epidemiologists around the globe have several crucial messages for the humanity in general and especially warning India for an expected third wave adversely affecting the children. We all are committed to help the nation in preventing further damages unfortunately being forced on us by unknown and unnatural sources yet being active around us. Considering the above scenario this issue of the bulletin has more space designated for communicable diseases focused on COVID-19 related thoughts. I think for years to come we will have to deal with after-effects of the pandemic. But updates on a series of other communicable and non-communicable diseases have to get their pending due and the highlighted epidemiological aspects of such crucial illnesses must be disseminated through the bulletin. Also, sharing of certain epidemiological issues related to health and nutrition of human being are essential. Health issues are no way less important than talking of diseases.

The editorial board of the bulletin, though still in making, would like to request the active members of EFI to come out of their hesitations in sharing with us the news and updates on the academic events, webinars, mini-conferences, seminars and workshops already organized (with a couple of photographs with brief abstract) and/or are to be organized by them in near future at local or regional levels. The bulletin has dedicated space ear-marked for the purpose to encourage awareness amongst the fellow members.

I feel grateful to the honorable contributors for sharing their advanced scientific thoughts to this issue of the bulletin. These articles of interest and also being time relevant would certainly provoke and enthuse the members of EFI. As pointed out earlier, EFI has a huge resource of wide-spectrum experts and therefore, I invite each member to actively participate and contribute articles of their areas of specialty with ideas to further enhance the levels as well broaden the scope of the contents of the Bulletin. The editorial column is already incorporated now and soon a workable editorial board should be in place after completing certain formalities.

Ajit Sahai

EFI Governing Body

Aims of EFI

To identify and promote areas of cooperation and understanding among researchers and like-minded organizations, individuals, scientific networks and other Governmental and Non-Governmental, National & International agencies which are contributing towards realizing the objectives of the Foundation.

Benefit of becoming a member of EFI

- Networking with renowned Epidemiology experts worldwide and partnership with Professional organizations in field of Epidemiology.
- Receiving announcements of EFI activities.
- Eligibility to receive travel scholarship / support for attending EFI sponsored courses / meeting.
- Reduced registration fees for attending EFI Training Courses, CME, Regional meeting and Annual Conference.
- Joint membership of International Epidemiological Association (IEA)

Types of members

- Life Memberships
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IEA joint memberships with EFI
Special rates for joint membership for regular member is 25 USD and for ECE is 10 USD do visit http://www.ieaweb.org/ for more details.

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Obituary: Prof Vinod K Srivastava

Professor Vinod K Srivastava – founder President of Epidemiology Foundation of India, had been a senior faculty in Community Medicine for decades. While continuing as the Principal of the Prasad Institute of Medical Sciences, Lucknow, India, he breathed his last on 18th April 2021 during his sleep to continue his journey in another World.

Professor Vinod K Srivastava had many qualities. A renowned epidemiologist and a well-known public health specialist. Professor Srivastava was a towering personality in the field of Epidemiology having several exemplary qualities. As a man of great sense of responsibility and commitment and throughout being sincere and loyal to his duties, had a very high order of integrity. Always respectful towards his friends and colleagues, particularly to his seniors and was very helpful to his students & friends.

Professor Srivastava joined KGMU as a MBBS medical student in 1967 and completed his MD (Community Medicine) in 1977. As an alumni of KGMU Lucknow, he devoted major part of his professional career to his own alma-mater and superannuated as a Professor of Community Medicine and Chair Dept. of Hospital Administration. He occupied several important academic and research positions in India viz. Director, Regional Medical Research Centre, NE Region (Indian Council of Medical Research), Dibrugarh and Director, State Institute of Health and Family Welfare, Lucknow, India; Director, Integral Institute of Medical Sciences and Research & Dean, Faculty of Medicine, Integral University, Lucknow. Director, Hind Institutes of Medical Sciences, Lucknow. He had been the honourable Vice-Chancellor of Texila American University, Georgetown, Guyana, SA.

Professor Srivastava had been the past National President of Indian Public Health Association and also President of Indian Association of Preventive and Social Medicine. He had a long association with International Epidemiology Association (IEA) and served as Regional Councilor for South East Asia Region (2008-14) and Secretary - IEA during 2014-17. Taking it as a mission he continuously promoted epidemiological activities in South East Asia region through national professional associations in Sri Lanka, Nepal, Thailand, Korea and Indonesia.

The EFI will always remember Professor Vinod Srivastava, it's founder President for his significant contributions. We all pay our sincere tributes to him. He will always remain in our hearts!

EFI Foundation Management Committee

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EDITORIAL

Non-alcoholic fatty liver disease as an independent risk factor for cardio-vascular diseases: an association with grave implications in need of epidemiological prowess

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India is a country that is transitioning demographically. As the life expectancy increases, this shift is accompanied by an epidemiological transition with majority of disease burden attributed to non-communicable diseases, such as cardiovascular diseases. Non-alcoholic fatty Liver Disease (NAFLD) is an emerging risk factor for other non-communicable diseases, and it is imperative that such emerging risk factors be accorded due investigation in the form of methodologically robust cohort studies, and these findings be confirmed by randomized controlled trials yielding experimental evidence of reduced CVD events with treatment of NAFLD.

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease worldwide, with a global prevalence of 25% (1). There is evidence that the prevalence of NAFLD is rising, and is accompanied by an increase in adverse liver related outcomes such as liver cirrhosis and hepatocellular carcinoma. (2).

NAFLD is not merely a 'the hepatic manifestation of metabolic syndrome' as was perceived historically. There is growing evidence that NAFLD may independently be a pivotal factor for the development of other manifestations of metabolic syndrome; particularly cardiovascular diseases.

From a pathogenic perspective, NAFLD is strongly associated with insulin resistance and other features of the metabolic syndrome (MetS) (3). The underlying biological mechanism that links NAFLD to CVD is hypothesized to originate in the expanded visceral adipose tissue. The insulin resistance is a result of chronic inflammation that increases the circulation of pro-atherogenic mediators and the activation of two main intracellular transcription factor-signalling pathways, i.e., the nuclear factor kB and JNK pathway (4).

CVD is reported to be the leading cause of death in patients with NAFLD (5). However, the task of convincingly establishing NAFLD as an independent risk factor for CVD is fraught with methodological issues thatepidemiologistsare all too familiar with. NAFLD is strongly associated with dyslipidaemia, hypertension, diabetes and obesity, all known established risk factors for CVD (6). These shared risk factors form the potential for distortion in effects due to confounding. The disparate results from cohort studies have reflected this methodological challenge. Large cohort studies like Labenz et al (7) have identified NAFLD as a risk factor for

CVD on the basis of data from a large administrative database of primary care practices. On the other hand, Lauridsen et al (8) conducted a mendelian randomization study that used the PNPLA3 gene as an instrumental variable and concluded that high liver fat content was not causally associated with risk of CHD. The findings in either direction need to be replicated to inch closer to achieving a compelling body of evidence. Techniques such as mendelian randomization can be leveraged in more observational studies to clarify if this association is a by-product of confounding by shared risk factors.

While the establishment of causality is a goal that may seem unobtainable in most circumstances, this ongoing debate needs evidence from adequately powered and methodologically robust studies.Observational studies should be able to adequately deal with potential confounding by adjusting for such covariates.However, even observational studies with sophisticated analyses are no replacement for randomization. It is imperative to study therapies for NAFLD through the conduct of randomized controlled trials that report clinically relevant outcomes like cardiovascular disease. What also needs further study is where in the spectrum, from simple steatosis to NASH does the risk of CVD begin to rise.

Needless to say, the association of NAFLD with incident CVD has serious public health implications. Clinical and policy decisions with regard to risk stratification for cardiovascular diseases and population level screening would be informed by establishment of NAFLD as an independent risk factor for CVD. Seeing the high prevalence of NAFLD in the community and its rising burden, the time to catapult this to the forefront of epidemiological investigation is perhaps now.

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CME

Performance of Students of Public Health in Epidemiology Examinations – Who Is Accountable?

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In medical education, Community Medicine is one of the subjects, which provides theory, as well as, practical teaching & training in epidemiology to the students. In both graduate (MBBS) and postgraduate (MD/MPH) courses, when theory/practical examinations (written / viva) are held, epidemiology is an important component. Over last many years, as an examiner, it has been mine and others' observation that students often lack the basic understanding of the epidemiology.

In fact, whenever any epidemiology related question is asked in the theory examination, the students' answers mainly focus upon the distribution and determinants of the disease. Majority of them, fail to mention about the prevalence or incidence of the disease. Naturally, as an examiner, I deduct marks for this lapse. But then, this trend set me thinking about the gaps in our teaching. The answer was not difficult to locate. Actually, the students seem to have been confused because of a single, specific and popular definition of epidemiology taught to them, e.g., "The study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to the control of health problems".[1]

As a comparison, definition by an Indian expert from UK does mention about the extent of the disease, "Epidemiology is the science and craft that studies the pattern of disease in populations to help understand both their causes and the burden they impose. This information is applied to prevent, control or manage the problems under study". [2]

On scrutiny, it emerged that more than hundred definitions of epidemiology are there. For the benefit of the students, it is vital to clarify and explain the contents of these definitions. In fact, extent / burden of the disease should be the first basic concern of any epidemiologist or a public health expert, i.e., whether the disease is really a public health problem of concern deserving resource deployment for its control.

Lately, it has been seen that the bulk of our teaching of epidemiology gives undue emphasis on computer jugglery. Even some senior epidemiologists have lamented the obsession of the discipline experts on the RISK (determinants) detection methods rather than the health. Focus is mainly on sophisticated statistical applications using a plethora of packages.[3]

Some experts have identified more than 20 different terms and concepts in various definitions of epidemiology available in literature. Many definitions focused upon 'disease', while others mentioned 'health'. Causes or determinants were a part of many definitions, along with the distribution of the disease. Few definitions included natural history and prevention and control of the disease. 'Frequency of disease/ incidence/ prevalence / burden was a part of the definitions in few cases only'. [4, 5] Lilienfeld had mentioned earlier that there was no consensus among epidemiologists about the definitions.[6]

Apart from this, even the status of epidemiology as a 'true' science is often debated; it has been labeled by some as an 'inexact science'. It is told to be a set of tools used by other disciplines. Few experts also declare it as a form of journalism! This is because, it depends mainly on observational data with a focus on variables that

are difficult to quantify coupled with its interface with the 'soft' behavioral sciences. [7, 8] As a core public health science, epidemiology considers the role of multiple variables associated with human diseases, e.g., pathogens, human behavior dynamics, and the environment.

Epidemiology involves a multidisciplinary approach to describe health related problems (incidence, distribution) in humans for identifying their causes. In doing so, it provides requisite data for planning the health services for their prevention, control and treatment of and control of disease in a population. In addition to its role in disease surveillance and prevention, epidemiology also helps in gathering the data for understanding the health paradigm. It helps in health care need assessment; it quantifies our risks of acquiring any disease; it helps in prioritizing the deployment of existing resources for dealing with health problems. Above all, it considers society as the source for explaining health problems as well as the setting where their solutions are to be found. [9]

Epidemiology is a discipline which has evolved with the changes taking place in society in general as well as the emergence of new diseases or new related disciplines. So, it's teaching has to be flexible and up to date. For teachers, it is important to analyze the evolution of the content of its definitions. On their part, students of epidemiology often complain bitterly about the confusing way in which the fundamental concept and multiple definitions of epidemiology have been treated in the literature.

Moral of the story is that, if the performance of students of public health in epidemiology examinations is poor, the students are not at fault. It is a result of our deficiency as teachers. We have not been able to foster a consensus on a comprehensive definition of epidemiology which is not confusing. We can no longer give an excuse of epidemiology being an evolving discipline to justify the lack of a clear cut definition.

It also needs to be examined as to - Why definition issues plague Public Health discipline regularly? Even for Health Promotion and Public Health various new definitions have emerged. Singh had also highlighted in 2004, that there is a lot of confusion about the definitions, scope and contents of the terms related to Public Health.[10]

Actually, many issues are linked with the contents of the definition of epidemiology. It is a kind of turf war also. The issue is also linked with some basic questions, e.g., what is the role of an epidemiologist in the society in general and in the health care delivery system, in particular? How many of them are there in India? Who is can qualify as an epidemiologist? What are the basic qualifications of an epidemiologist? Whether their role is only diagnostic? Are they supposed to only suggest strategies for disease control? Are they expected to act also? Do they have a service area to practice their trade?

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A brief note on COVID-19 vaccine efficacy and 'Protection'

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Let us assume that "2 Companies Say Their Vaccines Are 95% Effective". What Does That Mean? You might assume that 95 out of every 100 people vaccinated will be protected from Covid-19. But that's not how the math works.

Brief methodology: Researchers vaccinate some people and give a placebo to others. They then wait for participants to get sick and look at how many of the illnesses came from each group. [Other 'methodological issues [following CONSORT guidelines - like 'How sample size was determined (Item 7a)', 'Randomization Sequence generation (Item 8a)', 'Allocation concealment (Item 9)', 'Blinding (Item 11a)'] were assumed/considered to have taken care of].

Vaccine Efficacy (VE) generally are expressed as a proportionate reduction in disease attack rate (AR) between the unvaccinated (ARU) and vaccinated (ARV), or can be calculated from the relative risk (RR) of disease among the vaccinated group

The basic formula is written as:

VE=[{ARU-ARV}/{ARU}] * 100%}

where

VE = Vaccine efficacy,

ARU = Attack rate of unvaccinated people,

ARV = Attack rate of vaccinated people.

An alternative, equivalent formulation of vaccine efficacy

VE=(1-RR) * 100%,

where

RR is the Relative Risk [also called Risk Ratio] of developing the disease for vaccinated people compared to unvaccinated people.

[note that VE is similar to Relative Risk Reduction (RRR) - a popular term/measure in epidemiology. Other known term/measure is Absolute Risk Reduction ARR={ARU-ARV}. Since (1 / ARR) is NNT (Number Needed to Treat), it may help better interpret it for clinicians]

{In the case of Pfizer (New York Times of 20th November, 2020), for example, the company recruited 43,661 volunteers and waited for 170 people to come down with symptoms of Covid-19 and then get a positive test. Out of these 170, 162 had received a placebo shot, and just eight had received the real vaccine. Pfizer's researchers calculated the fraction of volunteers in each group who got sick. Both fractions were small, but the fraction of unvaccinated volunteers who got sick was much bigger than the fraction of vaccinated ones. The scientists then determined the relative difference between those two fractions. Scientists express that difference with a value they call efficacy. {Vaccine efficacy by second/alternative formula (assuming 1:1 allocation ratio) = [1 – (8/162)] * 100 = 95% approximately}. If there's no difference between the vaccine and placebo groups, the efficacy is zero. If none of the sick people had been vaccinated, the efficacy is 100 percent. A 95 percent efficacy is certainly compelling evidence that a vaccine works well. But that number doesn't tell you what your chances are of becoming sick if you get vaccinated. And on its own, it also doesn't say how well the vaccine will bring down Covid-19}.

Vaccine efficacy was designed and calculated by Greenwood and Yule in 1915 for the cholera and typhoid vaccines. It is best measured using double-blind, randomized, clinical controlled trials, such that it is studied under "best case scenarios". Vaccine effectiveness differs from vaccine efficacy in that vaccine effectiveness shows how well a vaccine works when they are used in a bigger population whereas vaccine

efficacy shows how well a vaccine works in certain, often controlled, conditions. Although efficacy and effectiveness studies are both important when evaluating interventions [therapeutic or prophylactic], they serve distinct purposes and have different study designs. Unfortunately, the distinction between these two types of trials is often poorly understood. Efficacy of a regimen is its positive response rate in ideal conditions and effectiveness is the positive response rate in actual conditions.

Clinical trials are generally done in ideal conditions that do not exist in practice. The subjects are carefully chosen with strict inclusion and exclusion criteria, administration is done in standard conditions, efforts are made for full compliance, patients get full attention, the results are adjusted for dropouts and other missing observations, and the response is carefully assessed by experts. The actual performance of the regimen in practice may differ. Efficacy of a treatment is what is achieved in a trial that simulates optimal conditions, and effectiveness is what is achieved in practical conditions when the treatment [be it therapeutic or prophylactic] is actually prescribed. For clarity, the latter is sometimes called use-effectiveness.

Effectiveness could be lower than efficacy because of lack of compliance of the regimen due to cost or inconvenience, inadequate care, nonavailability of the drugs, etc. These rarely occur in a trial. Experience suggests that nearly three-fourths of the patients do not adhere to or persist with the full prescriptions. Thus, patients and manoeuvres adopted during a trial do not translate their results for patients at large. Consequently, such external validity of the trial results is not high. But clinical trials do establish the potential of a regimen to effect a change. Effectiveness, on the other hand, is a suitable indicator to decide whether or not to adopt that regimen in practice, or what to expect. For further details, see Singal et al. ['A primer on effectiveness and efficacy trials' Clinical and Translational Gastroenterology (2014) 5. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3912314/

95% vaccine efficacy means that instead of 1000 COVID-19 cases in a population of 100 000 {which is just like the radix of the life table [A life table is customarily constructed for a hypothetical cohort of 1, 00,000 new-born babies. This is called the radix of the life table. The radix is assumed to be closed to migration. Instead of 100000 if you take 2000000 or 50000, end result will remain same. It gets depleted only through death of its members]} without vaccine (from the placebo arm of the trial, approximately 1% would be ill with COVID-19) and we would expect 50 cases if VE is 95% [Verification: VE= [{(1000/100000) - (50/100000)}/ (1000/100000)] = [{(0.01)-0.0005)}/ (0.01)] = [{(0.0095)}/ (0.01)] =0.95 or VE= [{1-(50/1000)] = [(1-0.05)] =0.95]. That is, we would expect roughly 0·05% of vaccinated people would get diseased (which implies that 99·95% of the population is disease-free, at least for 3 months). This implies that the protection rate=99.95% {for the protection rate with 95% vaccine efficacy & 1% attack rate/case rate see a letter-to-editor on 'What does 95% vaccine efficacy mean?', [by Piero Olliaro of University of Oxford, Oxford OX3 7FZ, UK, at: www.thelancet.com/infection Vol 21 June 2021]}.

On these lines [of calculations], we will now prepare a table for 95, 90, 85, 80, 75 and 70% vaccine efficacy for the same size trial (for any size of trial, protection rate / percentage will remain same), a cumulated COVID-19 attack rate [case rate] over a period of 3 months of about 1 to 5% without a vaccine.

[note that protection rate proportion is one minus risk of disease in vaccinated group]

Attack/Case Rate (%)	Sample Size of Placebo group	Expected Number of cases in placebo group	Vaccine Efficacy (%)	Sample Size of vaccine group	Expected Number of cases in vaccine group	Protection Rate (%)
1	100000	1000	95	100000	50	99.95
1	100000	1000	90	100000	100	99.9
1	100000	1000	85	100000	150	99.85
1	100000	1000	80	100000	200	99.8
1	100000	1000	75	100000	250	99.75
1	100000	1000	70	100000	300	99.7
2	100000	2000	95	100000	100	99.9
2	100000	2000	90	100000	200	99.8
2	100000	2000	85	100000	300	99.7
2	100000	2000	80	100000	400	99.6
2	100000	2000	75	100000	500	99.5
2	100000	2000	70	100000	600	99.4
3	100000	3000	95	100000	150	99.85
3	100000	3000	90	100000	300	99.7
3	100000	3000	85	100000	450	99.55
3	100000	3000	80	100000	600	99.4
3	100000	3000	75	100000	750	99.25
3	100000	3000	70	100000	900	99.1
4	100000	4000	95	100000	200	99.8
4	100000	4000	90	100000	400	99.6
4	100000	4000	85	100000	600	99.4
4	100000	4000	80	100000	800	99.2
4	100000	4000	75	100000	1000	99
4	100000	4000	70	100000	1200	98.8
5	100000	5000	95	100000	250	99.75
5	100000	5000	90	100000	500	99.5
5	100000	5000	85	100000	750	99.25
5	100000	5000	80	100000	1000	99
5	100000	5000	75	100000	1250	98.75
5	100000	5000	70	100000	1500	98.5

Generally, such statistic (here VE) is presented with its Standard Error (SE) & Confidence Interval (CI). Since an alternative, equivalent formulation of vaccine efficacy

VE=(1-RR) * 100%

where RR is the Relative Risk of developing the disease for vaccinated people compared to unvaccinated people. From SE & CI of RR we can estimate both for VE as follows:

Suppose we display our data like in table given below

Disease developed in given period	Vaccination status	
	Given (Vaccinated Group)	Not given (Un-vaccinated Group)
Yes	A	B
No	C	D
Total	A+C	B+D

Then in terms of notation of above table

RR= [A/(A+C)] / [B/(B+D)].

Confidence interval for population value of Relative Risk (RR) is estimated through a logarithmic transformation. The standard error of loge RR is

SE (loge RR) = Sq. Root {[C / A(A+C)] + [B / B(B+D)] }.

This can also be written as

SE (loge RR) = Sq. Root { [1/A] – [1/(A+C)] + [1/B] – [1/(B+D)] }.

Then we calculate W = loge RR – [Z1-α/2 × SE (loge RR)] and

X = loge RR – [Z1-α/2 × SE (loge RR)],

where Z1-α/2 is the appropriate value from the standard normal distribution for the 100(1-α/2) percentile.

The confidence interval for the population value of RR is then given by exponentiating 'W' and 'X' i.e. eW to eX.

[Reference: page 58 of Altman DL, Machin D, Bryant TN, and Gardner MJ. 'Statistics with Confidence: Confidence Intervals and Statistical Guidelines' 2nd edition, BMJ Books, London, 2003]

Example: Let us consider the first situation given in table above [1% attack rate/case rate, sample size of placebo group=1 lakh and sample size of vaccine group=1 lakh, the expected number of cases in placebo group are 1000 and the expected number of cases in vaccine group are 50].

Suppose we display our data like in table below:

Disease developed in given period	Vaccination status	
	Given (Vaccinated Group)	Not given (Un-vaccinated Group)
Yes	A=50	B=1000
No	C=99950	D=99000
Total	A+C=100000	B+D=100000

Then [in terms of notation of above table]
RR= [50/100000)] / [1000/100000] =0.05.
Therefore, the Vaccine Efficacy is 95%

Confidence interval for population value of Relative Risk (RR) is estimated through a logarithmic transformation. The standard error of RR is 0.145 [after taking anti-log]. The 95% confidence interval for the population value of RR is 0.037 to 0.066. Therefore, the 95% confidence interval for the population value of VE [sample Vaccine Efficacy 95%] is 93.4% to 96.3%.

Now let us consider the sixth situation given in the table above which has 2% attack rate/case rate, sample size of placebo group=1 lakh and sample size of vaccine group=1 lakh, the expected number of cases in placebo group are 2000 and the expected number of cases in vaccine group are 100]. Vaccine Efficacy is still 95%. The standard error of RR is 0.049 and the 95% confidence interval for the population value of RR is 0.040 to 0.060. Therefore, the 95% confidence interval for the population value of VE [sample Vaccine Efficacy 95%] is 94% to 96.%. Not much difference. In both these situations CI are very narrow because n=100000 in both groups.

Now let us consider the situation where attack rate/case rate is 2%, but sample size of placebo group=1000 and sample size of vaccine group=1000 only. The expected number of cases in placebo group are 20 only and the expected number of cases in vaccine group is only one. Vaccine Efficacy is still 95%. The standard error of RR is 0.034 and the 95% confidence interval for the population value of RR is 0.005 to 0.249. Therefore, the 95% confidence interval for the population value of VE [sample Vaccine Efficacy 95%] is 75.1% to 99.5.%. Now for this situation CI is very wide because n=1000 only in both groups.

[SE & CI for RR in all situations are estimated by using computer software called 'Confidence Interval Analysis (CIA)' by BMJ Group, London, 2003].

Communicable Diseases

COVID-19 policy lessons for health systems strengthening in India

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In Apr May 2021, millions of Indians- in sheer desperation- in need of health services, pleaded for help on social media from the complete strangers; the family members stood the queues to fetch medical oxygen and medicines for their loved one; and nearly everything needed to fight a disease-- beds, ventilators, medicines, vaccines and the ambulances-- was in short supply. The health systems in India has struggled to mount a coordinated response to second wave of COVID-19 pandemic and fumbled at nearly every level and step. What is even more worrying, we ended up in this situation, in-spite of one year for planning. It is clearly the time for introspection and actions.

For years, health experts had demanded to strengthen health services and systems in India. Year after year, successive governments have ignored the health services. In recent years, political leaders and policy makers started to acknowledge the challenges and fresh policy commitments to strengthen health system were made. However, promises remained unfulfilled. In 2017, the national health policy (NHP) of India proposed, inter alia, to increase government spending on health to 2.5% of Gross domestic product (GDP) by year 2025. Four year's since then, at mid-point of target year, government spending on health has increased marginally from 1.15% to around 1.28% of GDP. This rate of increased allocation is not enough to achieve NHP target. The health services in India, in principle, are free for every citizen. However, when people visit a government health facility, they often return unsatisfied. Either a doctor is not available, or medicines are in short supply, in many cases both. Even poor 'vote by the feet' and attend private sector, paying from their pockets, at risk of getting impoverished.

Health researchers have argued that an assured provision of the promised health services, results in people having trust in health services and improve the utilization. However, government health facilities have nearly always failed in this 'assured provision' approach and the trust has continue to eroded, time and again, by fresh policy missteps. The announcement of vaccination for all adult citizen without 'assured supplies' of COVID-19 vaccines is another such example. A vaccination drive with potential to counter the pandemic, is in a shamble.

If what is happening now does not shake the political leadership and policy makers to immediately 'overhaul' and strengthen health systems in India, then we really don't know what would. Merely promises will not be enough, not anymore. Four areas of financial allocation, human resources, health leadership and bringing trust back in government health services should get immediate priority and urgent attention.

It is time, the union and state governments immediately increase the financial allocation for health, to bring country on track to achieve 2.5% of GDP for health by 2025. The state governments should allocate 8% of state budget for health. These were proposed in NHP 2017. Alongside, the financial management rules and guidelines, which are archaic and considered hurdle in fund utilization, need to be simplified. People are already facing hardships, and, in the ongoing pandemic, the governments should take full responsibility of all COVID-19 related expenditure for every citizen, whether treated in private or government facility.

Amongst the biggest challenge of government health system in India, is shortage of health staff. There are many vacancies, a large of health staff is contractual, the regular positions are vacant for decades, old salary scales have not been revised for decades with wide variations between state governments. The working conditions for health staff are not conducive. The government health facilities fail to attract and retain staff. It is not enough to call health workers 'Corona Warrior', it is time that the salary scales are revised, vacancies are filled at every level and the health facilities are made functional.

For decades, we have witnessed the techno-bureaucratic leadership in health. Much of the pandemic response followed the similar pattern. It is time to give a serious policy consideration to establish Indian Health Services- with two cadres of medical services and public health, on the line of administrative services. As an immediate measure, the positions of health secretaries at both union and state levels should be filled by the subject experts. Health is one sector where lateral entry should be allowed. The professionals with specialized skills should be engaged in health services designing, planning, management and implementation, up to lowest level of healthcare facility, paid at the market rate and performance assessed on outcome linked parameters, to renew the contracts. It is time that independent subject experts on the wider areas of health linked expertise, are engaged in health policy and strategy formulation, planning and implementation.

The pandemic has severely dented the trust in government health services. The trust of the citizen cannot be gained by empty promises but need actions at ground. To regain the trust, the government needs to acknowledge the mistakes and show that it is open to take corrective measures. In one of the first such acknowledgement, the union government revised liberalized vaccine policy on 7 June 2021. Once again, the COVID-19 vaccines are being purchased and paid by central government (as single purchaser) at uniform price and made available to the states. COVID-19 vaccination is just an example and many such policy corrections are needed in various areas of health sector.

Homo Neanderthals- our closest ancestor who became extinct around 40,000 years ago- were not considered social --lived in smaller groups and practiced cannibalism. However, archeological evidence of trauma which would not have healed if not cared for, have made experts and researchers to concluded that when it came to health needs of each other, they were compassionate. And that what Indian politicians and health policy makers need learn from our ancestors: compassion.

Genomic Surveillance for SARS-CoV-2- A Tool for Public Health Action

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Introduction

SARS-CoV-2 being RNA virus has tendency to mutate. In the second half of 2020 and in early 2021, SARS-CoV-2 variants were reported worldwide which had more transmissible tendency than existing strains and also less likely susceptible to neutralization by host antibodies.[1–3] It prompted the scientific community to develop a genomic sequence surveillance system to ensure rapid detection and characterization of variants of concern.[4–7] The growing understanding of how sequence information can contribute to improved public health is driving global investments in sequencing facilities and programmes and to initiate the appropriate country specific public health responses.[8]

In February 2020, mutation with G614 spike protein strains was reported from various countries as a major shift in SARS-CoV-2. The change in G614 spike protein position lead to enhanced viral replication and higher transmissibility, however, the evidence to cause more severe disease or to evade host immune responses was lacking.[9]

In December 2020, a new variant with multiple mutations (B.1.1.7) was reported from United Kingdom (UK). By early 2021, this UK variant spread to various parts of UK and to many other countries also & in some it became the dominant strain. The B.1.1.7 was found to be higher in all age groups and in all geographic regions of the UK due to high secondary attack rate however remained inconclusive for increased severity of infection.[10] The variant has been reported from India also from Punjab & Delhi.[11]

Another 'variant of concern' (B.1.351) was first identified in South Africa as the dominant strain in the country. It also had higher transmissibility and the variant appears to be less effectively neutralized by host antibodies.[10] Soon It was also detected in other countries. It has been reported from India also.[11]

In January 2021, a 'variant of concern' (B.1.1.248/B1.1.28/P1) was reported from Japan in a

traveller from Brazil. This variant, with 12 mutations in the viral spike protein, had changes likely to affect antibody neutralization. It has been reported from India also.[12]

Genomic Surveillance:

Genomic surveillance of SARS- CoV-2 is important for understanding the evolution of viral pathogens and for changes in transmissibility, virulence, and disease clinical course. It requires global coordination to monitor emerging variants. We have to develop a robust and coordinated global action to identify and characterize emerging variants otherwise the societies will have a threat of setbacks in health care and economy.[3,12]

The application of Genomic Surveillance of SARS-CoV-2 has a varied but insufficient response globally in the changing pandemic scenario. Many rich countries such as Iceland, Luxemburg and Japan have reported high level of viral genomic sequencing, on the other hand, countries like Iraq and Venezuela have reported

fewer sequencing. In Africa so many countries have no sequencing at all but at the same time few African countries like Zambia, Sierra Leone, Equatorial Guinea have reported higher sequencing in comparison to France and Italy and to even USA. The African Center for Disease Control and Prevention has moved swiftly to initiate COVID-19 sequencing.[2,4–7]

The COVID-19 Genomics UK Consortium (COG-UK), launched in April 2020 has grown up and supports 16 sequencing hub across the country including the four public health agencies, researchers and academic Partners. The consortium has completely changed the landscape of how to do pathogen sequencing. Earlier the sequencing took place only in the reference laboratories only but now the consortium expanded and has sequenced over 140,000 genomes.[5]

The Center for Disease Control (CDC), USA launched the genomic consortium of laboratories as SPHERES (SARS-CoV-2 Sequencing for Public Health Emergency Response, Epidemiology, and Surveillance) consortium which consists of more than 200 institutions, industries, Non-Governmental Organizations and Public Health Agencies.[4]

In India, in December 2020 the Ministry of Health and Family Welfare announced the Indian SARS-COV-2 Genomics Consortium (INSACOG) with 10 prominent laboratories as partners. Further, the Ministry also announced that INSACOG will have 5% of all COVID positive samples from every State and 100% of all positive samples from international travellers which will be collected on weekly basis for sequencing. However, the progress has been so far slow.[6]

Genomic surveillance already well established like the Global Influenza Surveillance and Response System (GISRS) and the Global initiative on sharing all influenza data (GISAID) genomic database.[13,14] In the Covid-19 pandemic the other platforms are also analysing data and exploring phylogenetic relatedness, including Phylogenetic Assignment of Named Global Outbreak (PANGO) lineages is software tool developed by members of the Rambaut Lab, GISAID clade and Nextstrain (a collaboration between researchers in Seattle, USA and Basel, Switzerland) clade.[15,16] WHO issued guidelines, in Jan 2021, on the use of whole genome sequencing for SARS-CoV-2, including advice on which samples required to be given priority for sequencing, as well as a detailed implementation guide.[3]

Environmental surveillance in wastewater and sludge

The wastewater monitoring is an important activity for tracing the silent circulation of for pathogens such as poliovirus viruses in a community. The approach helps in detecting circulation (before the initial patients have been clinically detected), estimate prevalence, and understand the genetic linkage and diversity. Many countries have demonstrated molecular detection of SARS-CoV-2 RNA in wastewater. Therefore, environmental surveillance is a promising approach, to identify unrecognized carriers and serve as an “early warning” system for SARS-CoV-2 or changes in prevalence especially in low prevalence settings.[8]

SARS-CoV-2 Variants Classification:

WHO has categorized the variants as ‘variants of concern’ (VOC), ‘variants of interest’ (VOI), and ‘variants of high consequence” (VOHC). To date, ‘variants of concern’ and ‘variant of interest’ as shown in Table- 1 & Table-2, have shown

evidence to affect transmissibility and, to some extent, antibody neutralization, but not for disease severity.[17–20]

Variants of Concern[20,21]

A SARS-CoV-2 variant that meets the definition of a VOI and through a comparative assessment, has been demonstrated to be associated with one or more of the following changes at a degree of global public health significance:

- Increase in transmissibility or detrimental change in COVID-19 epidemiology; or
- Increase in virulence or change in clinical disease presentation; or
- Decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics.

Possible attributes of a variant of concern:[20]

In addition to the possible attributes of a variant of interest

- Evidence of impact on diagnostics, treatments, or vaccines
- Widespread interference with diagnostic test
- Evidence of substantially decreased susceptibility to one or more class of therapies
- Evidence of significant decreased neutralization by antibodies generated during previous infection or vaccination
- Evidence of reduced vaccine-induced protection from severe disease
- Evidence of increased transmissibility
- Evidence of increased disease severity

Table 1: SARS-Cov-2 Variants of Concern (VOCs), as of 15 June 2021[17]

WHO Label	Pango Lineage	Date of designation
Alpha	B.1.1.7	18-Dec-2020
Beta	B.1.351	18-Dec-2020
Gamma	P.1	11-Jan-2021
Delta	B.1.617.2	VOI: 4-Apr-2021 VOC: 11-May-2021

Now a days the Delta plus variant is in news which is characterised by B.1.617.2 variant acquiring another mutation, K417N, it was also reported in the B.1.351 or Beta variant of concern. The mutation is in the spike protein of Sars-CoV-2, which helps the virus enter and infect the human cells. The earliest sequence of this genome was found in Europe in late March 2021. Experts stressed the need for more studies on the 'Delta plus' variant before reaching any conclusion on its transmissibility and ability to evade pre-existing immunity, built up either by vaccination or infection with the original Sars-CoV-2 strain. According to INSACOG (Indian SARS-CoV-2 Genomic Consortia), the Delta Plus shows "increased transmissibility, stronger binding to receptors of lung cells and potentially reduced monoclonal antibody response".[17–19,22]

Variants of Interest [20,21]

A SARS-CoV-2 isolate is a Variant of Interest (VOI) if, compared to a reference isolate, its genome has mutations with established or suspected phenotypic implications, and either:

- has been identified to cause community transmission/multiple COVID-19 cases/clusters, or has been detected in multiple countries; OR
- is otherwise assessed to be a VOI by WHO in consultation with the WHO SARS-CoV-2 Virus Evolution Working Group.

Possible attributes of a variant of interest:[20]

- Specific genetic markers that are predicted to affect transmission, diagnostics, therapeutics, or immune escape
- Evidence that it is the cause of an increased proportion of cases or unique outbreak clusters

Table 2: SARS-Cov-2 Variants of Interest (VOIs), as of 15 June 2021[17]

WHO Label	Pango Lineage	Date of designation
Epsilon	B.1.427/ B.1.429	5-Mar-2021
Zeta	P.2	17-Mar-2021
Eta	B.1.525	17-Mar-2021
Theta	P.3	24-Mar-2021
Lota	B.1.526	24-Mar-2021
Kappa	B.1.617.1	4-Apr-2021
Lambda	C.37	14-Jun-2021

Variant of High Consequence[20]

A variant of high consequence has clear evidence that prevention measures or medical counter measures (MCMs) have significantly reduced effectiveness relative to previously circulating variants.

Possible attributes of a variant of high consequence:[20]

In addition to the possible attributes of a variant of concern, impact on Medical Counter measures (MCM)

- Demonstrated failure of diagnostics
- Evidence to suggest a significantly reduction in vaccine effectiveness, a disproportionately high number of vaccine breakthrough cases, or very low vaccine-induced protection against severe disease
- Significantly reduced susceptibility to multiple Emergency Use Authorization (EUA) or approved therapeutics
- More severe clinical disease and increased hospitalizations

A variant of high consequence would require notification to WHO under the International Health Regulations, an announcement of strategies to prevent or contain transmission, and recommendations to update treatments and vaccines. *Currently there are no SARS-CoV-2 variants that rise to the level of high consequence.*[20]

Importance of Genomic Surveillance in Public Health[3,8]

CDC and its public health partners have been involved in routine analysis of genetic sequence which helped to identify and characterize variant viruses. They either identified new ones in the U.S. or identified those which were already identified abroad and have also investigated the variants impact on COVID-19 disease severity as well as the effectiveness of vaccines, treatment, and diagnostic tests. Surveillance of emerging genetic variants may help in detecting variants with:

- Ability to spread more quickly in people
- Ability to cause either milder or more severe disease in people
- Ability to evade detection by specific diagnostic tests Many commercial nucleic acid amplification tests (NAATs) that use reverse transcription polymerase chain reaction (RT-PCR) have multiple targets to detect the virus, such that even if a mutation impacts one of the targets, the other RT-PCR targets

will still work. However, there are some tests that rely on only one target, and mutations may impact their ability to work.

- Decreased susceptibility to medical therapies that employ monoclonal antibodies, such therapy involves specifically designed antibodies that target regions of the virus to block infection.
- Ability to evade natural or vaccine-induced immunity Both natural infection with and vaccination against SARS-CoV-2 produce a "polyclonal" antibody response that targets several parts of the spike protein. The virus would need to accumulate significant mutations in the spike protein to evade immunity induced by vaccines or by natural infection.

Among these possibilities, the ability to evade vaccine-induced immunity would be the most concerning. There is no definitive evidence yet that this is occurring, but scientists are closely evaluating this possibility.(23)

Application/s of Genomic surveillance of SARS-CoV-2 to combat COVID-19 pandemic

Understanding the biology (3,8,12)

- Genomic surveillance helps to unearth the potential impact of genetic mutations on the biology of variant SARS-CoV-2 strains. In particular, exploring the impact of variants on transmission, sensitivity to host immune responses, immune escape mechanisms, pathogenicity and response to therapeutics and vaccines will be key to inform the public health measures and response to the COVID-19 pandemic.
- Tracking the evolution through genomic surveillance will help to understand the forces driving the emergence and spread of variants, including the selection pressures exerted by use of vaccines, antivirals and other therapeutics, and other control measures. Genomic sequencing could be used to support surveillance for variants that may confer antiviral resistance or allow immune escape. Genomic surveillance may be useful in exploring the impact of intra-host diversity on antiviral resistance and immune escape. Genetic sequencing of specific regions of interest, such as the spike gene, may be sufficient to assess the prevalence of specific known variants in pre-identified regions.

Understanding the epidemiology (3,8,12)

- Tracking the evolution of SARS-CoV-2 pandemic globally is critical to understand how variants are contributing to changing epidemiological parameters of disease in terms of reproduction number, risk of reinfection and disease severity including mortality.
- Tracking the evolution will also be important to model the future waves during the pandemic so as to predict scale of outbreak over time. Identifying period/s with potential peak/s, expected number of cases, duration of entire wave will be pivotal so as to ensure optimal health system preparedness for responding to the health needs of the population.
- Identifying change in or additional modes of transmission for the viral agent (e.g., droplet to droplet nuclei or

transmission through sewage systems) will be the key if appropriate preventive public health measures are to be initiated and or strengthened.

Improving diagnostics and therapeutics (3,8,12)

- As SARS-CoV-2 continues to acquire genetic changes over time during the pandemic, continued generation and sharing of virus genomes will be vital for monitoring the expected sensitivity of the various diagnostic assays in different locations. Consistent failure to detect a prevalent SARS-CoV-2 variants in several clinical samples, or emergence of differences in the sensitivity of assays against the established variants, should be the trigger for sequencing of the virus genome or target gene to identify the possible cause and newer variants.
- The development of rapid, inexpensive and sensitive nucleic acid amplification tests for routine molecular detection of SARS-CoV-2 including its variants need to be prioritized to break the chain of infection.
- Continual assessment of genomic diversity, including in antigenically important sites that may be under selection, could help identify plausible candidate sites that might affect the efficacy of serological assays and achievement of critical levels for achieving herd immunity.
- Genetic and structural information can reveal similarities in proteolytic and replication pathways between SARS-CoV-2 and other viruses for which antiviral therapy is already available, and therefore help to determine which existing antivirals might be repurposed.

Understanding clinical implications (3,8,12)

- Understanding clinical impacts of infection with SARS-CoV-2 variants including in special populations such as children, pregnant women and immunosuppressed will be critical if impact of the pandemic on human health and mortality are to be minimized.
- Studies need to examine the effects of variants on both protective and harmful immune responses, and on responses to therapeutics.

Supporting vaccine development (3,8,12)

- SARS-CoV-2 genome sequences have been used in the design of candidate vaccines. Several candidate vaccines against SARS-CoV-2 have been designed and evaluated clinically. Continued tracking of variants through genomic sequencing for identifying viral proteins/parts that are antigenic and can help vaccine development will be critical as newer vaccines are developed and tested.
- Global genomic surveillance systems are required to assess the impact of variants on vaccine effectiveness. Tracking a cohort of vaccinated individuals will be important to identify immune escape mechanism, breakthrough infections in those who are vaccinated and unexpected clustering of COVID-19 cases in populations with high levels of vaccine coverage.

The speed from genomic sequencing and surveillance will be crucial and should be available to inform real-time decision-making if we have to maximize the impact of genomic surveillance data. We have limited options to face the challenge of expected third wave of covid-19. The genomic surveillance augmentation along with enhance vaccination programme coupled with appropriate covid behaviour will have to be promoted as public health measures to minimize the effect.

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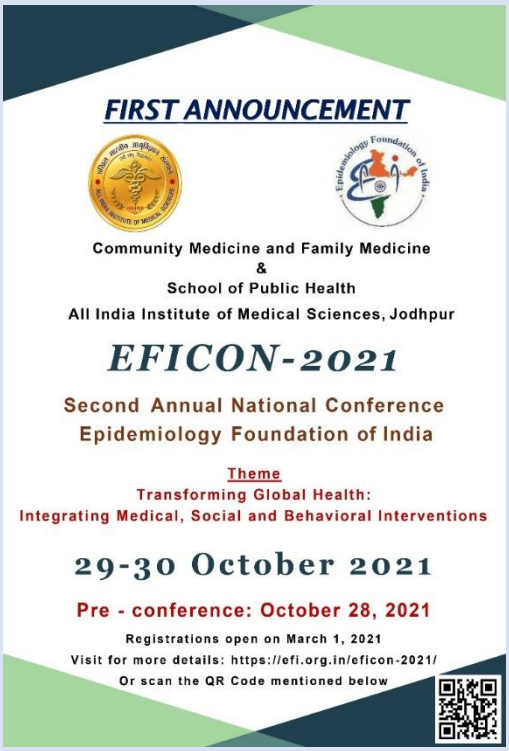
There is no conflict of interest and not funded from any source

News and Events

EFICON 2021



IPHACON 2021

WORLD CONGRESS OF EPIDEMIOLOGY 2021

WCE 2021
WORLD CONGRESS OF EPIDEMIOLOGY

The World Congress of Epidemiology (WCE) is held every 3 years by the International Association of Epidemiology (IEA). This year it will be held from 3-6th September 2021 virtually from Melbourne, Australia

Epi Monitor

http://www.epimonitor.net/PrintVersion/June%202021/Final-June-2021-The-Epidemiology-Monitor.pdf

epimonitor
THE EPIDEMIOLOGY MONITOR
A monthly update covering people, events, research and key developments

Point-Counterpoint Article Highlights Enduring Tension About The Proper Role Of Epidemiologists In Public Health

Fact Finders Only Or Fact Purveyors Also?

Should epidemiologists be devoted primarily to producing findings and publishing them objectively or should they also encourage the use of their findings in formulating evidence-informed control measures? This question was posed almost 40 years ago in the early days of The Epidemiology Monitor (October 1982) by a Florida-based epidemiologist who encountered resistance to implementing sanitary control measures. (See reprint this issue).

He had recommended these measures based on his investigation of a foodborne outbreak at a health care facility. As reported in letters to the editor at the time, the epidemiologist wondered to what extent he had a responsibility to be simply "an attack rate calculator" or also "a hell raiser" so that his data-based recommendations to protect the at-risk population would be adopted.

- Point con't on page 5

Expert Group Forecasts That SARS-CoV-2 Is Here To Stay

Enhanced Outbreak Control Strategy Is Proposed To Lessen Impact And Return To Relative Normalcy

Writing in a recent issue of *Foreign Affairs*, Larry Brilliant an epidemiologist and Chief Executive Officer of Pandefense Advisory and five other health professionals with varying backgrounds and expertise in epidemiology, infectious disease and other subject matters have assessed the status of the pandemic in the world, the international response to it, and given their opinions of what the most likely future of the disease will be. The article is entitled "The Forever Virus--A Strategy for the Long Fight Against COVID-19".

Here To Stay

They begin their assessment exclaiming

- Strategy cont'd on page 2

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