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## Preface

We would like to present, with great pleasure, the inaugural volume-6, Issue-9, September 2020, of a scholarly journal, *International Multispecialty Journal of Health*. This journal is part of the AD Publications series *in the field of Medical, Health and Pharmaceutical Research Development*, and is devoted to the gamut of Medical, Health and Pharmaceutical issues, from theoretical aspects to application-dependent studies and the validation of emerging technologies.

This journal was envisioned and founded to represent the growing needs of Medical, Health and Pharmaceutical as an emerging and increasingly vital field, now widely recognized as an integral part of scientific and technical statistics investigations. Its mission is to become a voice of the Medical, Health and Pharmaceutical community, addressing researchers and practitioners in below areas

### **Clinical Specialty and Super-specialty Medical Science:**

It includes articles related to General Medicine, General Surgery, Gynecology & Obstetrics, Pediatrics, Anesthesia, Ophthalmology, Orthopedics, Otorhinolaryngology (ENT), Physical Medicine & Rehabilitation, Dermatology & Venereology, Psychiatry, Radio Diagnosis, Cardiology Medicine, Cardiothoracic Surgery, Neurology Medicine, Neurosurgery, Pediatric Surgery, Plastic Surgery, Gastroenterology, Gastrointestinal Surgery, Pulmonary Medicine, Immunology & Immunogenetics, Transfusion Medicine (Blood Bank), Hematology, Biomedical Engineering, Biophysics, Biostatistics, Biotechnology, Health Administration, Health Planning and Management, Hospital Management, Nephrology, Urology, Endocrinology, Reproductive Biology, Radiotherapy, Oncology and Geriatric Medicine.

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It includes articles related to Pathology, Microbiology, Forensic Medicine and Toxicology, Community Medicine and Pharmacology.

### **Basic Medical Science:**

It includes articles related to Anatomy, Physiology and Biochemistry.

### **Spiritual Health Science:**

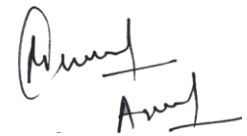
It includes articles related to Yoga, Meditation, Pranayam and Chakra-healing.

Each article in this issue provides an example of a concrete industrial application or a case study of the presented methodology to amplify the impact of the contribution. We are very thankful to everybody within

that community who supported the idea of creating a new Research with *IMJ Health*. We are certain that this issue will be followed by many others, reporting new developments in the Medical, Health and Pharmaceutical Research Science field. This issue would not have been possible without the great support of the Reviewer, Editorial Board members and also with our Advisory Board Members, and we would like to express our sincere thanks to all of them. We would also like to express our gratitude to the editorial staff of AD Publications, who supported us at every stage of the project. It is our hope that this fine collection of articles will be a valuable resource for *IMJ Health* readers and will stimulate further research into the vibrant area of Medical, Health and Pharmaceutical Research.



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He is recipient of Prof. Shiv Gautam oration award by Indian Psychiatric Society. He has done training in YMRS at Monte Carlo and BPRS at Singapore. He has been President Indian Psychiatric Society, Rajasthan State Branch. He is author of "Psycho Somatic Disorder" chapter in 1st edition post graduate text book of Psychiatry by Vyas and Ahuja. He has also worked with National Mental Health Programme and has a lot of publication.

**Research Area:** Community Mental Health, Psycho somatic and liaison Psychiatry.

## **Dr. Lokendra Sharma**

Dr. Lokendra Sharma is Associate Professor Pharmacology and working as Nodal officer of SMS Medical College, Jaipur.

He is recipient of WHO Fellowship award on Poison Patient Management at Vietnam. He is resource faculty for Experimental Toxicology and Basic Course for Medical Education. He is presented and published a lot of research articles at national and international level.

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## **Dr. Anuradha Yadav**

Dr. Anuradha Yadav is working as Professor Physiology, SMS Medical College, Jaipur (Rajsthan) India. She is a popular medical teacher and research scholar who had many publications in indexed journals.

**Research Area:** CVS & CNS physiology, Medical Education and Spiritual Health.

## **Dr. Rajeev Yadav**

Dr. Rajeev Yadav is working as Associate Professor Community Medicine, SMS Medical College, Jaipur (Rajsthan) India. He is member of Research Review Board of the Institute.

He has authored a book entitled "Community Medicine: Practcal Guide and Logbook".

**Research Area:** His area of Interest are Epidemiology, Biostatistics and Spiritual Health.

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Professor and Head in the Department of Oncology, AIIMS, Bhubaneswar.

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**Research Area:** Brachytherapy, Total Skin Electron Irradiation, Palliative Radiotherapy, Stereotactic & Conformal radiotherapy, Radiation Cell Biology, Cancer Genetics.

## **Dr. Praveen Mathur**

Dr. Praveen Mathur is working as Professor- Pediatric Surgery and is recipient of Commonwealth Fellowship in Pediatric Laparoscopy from Uk and fellowship award in minimal access Surgery (FMAS). He has done Clinical observer ship in the Department of Pediatric Surgery, Johns Hopkins University, Baltimore, USA. (2008). He has presented and published a number of research articles at national and international level. He is reviewer of prestigious Journal of Pediatric Surgery (JPS) and World Journal of Gastroenterology, Journal of neonatal Surgery (JNS).

**Research Area:** Pediatric Surgery & Laparoscopy.

### **Dr. Lokendra Sharma**

Dr. Lokendra Sharma is Associate Professor Pharmacology and working as Nodal officer of SMS Medical College, Jaipur.

He is recipient of WHO Fellowship award on Poison Patient Management at Vietnam. He is resource faculty for Experimental Toxicology and Basic Course for Medical Education. He is presented and published a lot of research articles at national and international level.

**Research Area:** PHARMACOLOGY.

### **Dr Rajeev Sharma (MS; FMAS; FIMSA;FCLS)**

He is working as Professor, Department of Surgery, Government Medical College, Chandigarh, India. He has done FMAS, FIMSA and FCLS along with MS (Gen Surgery).

He has about 50 international and national publications to his credit. He has held various positions in the Association of Minimal Access Surgeons of India (AMASI) from time to time. He has also acted as instructor of various AMASI skill courses held at different places in India. He has established Surgical Technique learning centre at GMCH Chandigarh for imparting training to the budding surgeons in the field of minimal access surgery. He is also the reviewer in the subject in various journals.

**Research Area:** Minimal Access Surgery.

### **Dr Anshu Sharma (MS ANATOMY)**

She is Presently working as assistant professor in the department of Anatomy, GMCH, Chandigarh. She has many publications in various national and international journals. She is executive member of Anatomical Society of India (ASI) and North Chapter of ASI. She is also a member of editorial board of Journal of Medical College Chandigarh.

**Research Area:** Congenital Malformation, Developmental Anatomy.

### **Dr. Rajeev Yadav**

Dr. Rajeev Yadav is working as Associate Professor Community Medicine, SMS Medical College, Jaipur (Rajsthan) India. He is member of Research Review Board of the Institute.

He has authored a book entitled "Community Medicine: Practical Guide and Logbook".

**Research Area:** His areas of Interest are Epidemiology, Biostatistics and Spiritual Health.

### **Dr. Dilip Ramlakhyani**

Dr. Dilip Ramlakhyani working as Associate professor Pathology and member of IT Committee of Sawai Man Singh Medical College, Jaipur (Raj) India. He has published many articles in indexed journals.

### **Dr. Virendra Singh**

Dr. Virendra Singh worked as Supernatant and head of department of Pulmonary Medicine, SMS Medical College, Jaipur (Rajasthan) India.

He has gone abroad for many training courses and to present research papers. He had been chairman of Research Review Board of SMS Medical College, Jaipur. He is a great research scholar and had published book related to his faculty and had many publications in indexed journals.

### **Dr. Mahesh Sharma**

Dr. Mahesh Sharma is a Principle specialist General Surgery in Rajasthan State Government, India. He has been PMO of district hospitals for more than 15 years. He has gone abroad as observer of many of training related to his speciality. He has published and present many research paper in India as well as abroad.

He has developed Spiritual Health Assessment Scale (SHAS) with Dr. Kusum Gaur.

**Research Area:** General Surgery, Health and Hospital management and Spiritual Health.

### **Dr. Ravindra Manohar**

Professor Community Medicine, working as head of department of PSM, SMS Medical College, Jaipur (Rajasthan) India.

Previously he has worked in BP Kiorala Institute of Medical Sciences, Nepal. He has visited CDC Atlántica for a Statistical workshop. He has been convener of MBBS and PG exams. He is a research scholar and had many publications in indexed journals.

### **Dr. Praveen Mathur**

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**Research Area:** Pediatric Surgery & Laparoscopy.

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# Maternal health care services utilization amidst Covid-19 lockdown: retrospective study

Sandhya Budhathoki<sup>1\*</sup>, Dr. Bibhuti Adhikari<sup>2</sup>, Dr. Rupesh Ramtel<sup>3</sup>

<sup>\*1</sup>Lecturer in Nursing, Nobel College, Sinamangal Rd, Kathmandu 44600, Nepal

<sup>2,3</sup>MBBS Doctor, Kathmandu Medical College, Sinamangal, Kathmandu 44600, Nepal

## **Abstract—**

**Objective:** The objective was to find the changes in maternal health care utilization.

**Design:** Retrospective design was adopted.

**Setting:** Study was conducted in Damak, Nepal.

**Methods:** Data from four hospitals was retrieved for fiscal year 2076/77 (July 14,2019 - June 14 2020). Trend analysis was done.

**Results :** Study showed a decline in utilization of overall maternal health care during the months of Lockdown. The utilization of antenatal care services has declined in the beginning of Lockdown but shows an increasing trend in the month of May-June. The number of Normal deliveries has declining trend since the beginning of Lockdown. The number of Caeserean Section declined during (March 14-April 12) and slightly increased in Bhaishak (April 13-May 13), but reduced again in the month of Jestha (may13-June14). The number of permanent family planning service use reduced in Chaitra (March 14-April 12), increased very slightly in Bhaishak(April 13-May 13), and declined again in the month of Jestha(may13-June14). The utilization of temporary family planning method and immunization has increased in the later month of Lockdown.

**Conclusion:** This decline in utilization may increase the maternal morbidity and mortality rates.

**Keywords:** Maternal health services, COVID-19 lockdown, Nepal.

## I. INTRODUCTION

Corona virus is the ongoing international pandemic which started at Wuhan City, Hubei province of china on December. The number of infected people with Corona virus worldwide as of July, 2020 is 6,421,255 with mortality up to 3,79,055.<sup>1</sup> In Nepal, first case of Corona Virus was detected in January with increasing cases up to 13248 as of June, 2020.<sup>2</sup> As a preventive measure, Nepal has been in lockdown since the month of Chaitra,2076 (March,2020).

Maternal Mortality before the pandemic was 229 women/100,000 births according to the 2019 data of Family Welfare Division of Department of Health Services in Nepal. Even with decreasing MMR from 539 in 1996 to 239 in 2016, still 58 per cent of births in Nepal were attended by skilled health personnel before the lockdown.<sup>2,3</sup> Now, due to movement restrictions, transportation disruptions, and fear of being exposed to the virus, women are facing even more barriers to accessing maternal health care.<sup>3</sup>

Only around one fourth of women are seeking maternity services at Kathmandu Model Hospital after the lockdown started. Over 60 to 80 women used to visit the hospital's out-patient department every day

prior to the lockdown but now only 15 to 20 women are visiting. Women are visiting the hospitals for only emergency services.

The number of Institutional deliveries have also decreased all over the country, which shows that women are giving birth at home, which might possess a serious threat to mother's and newborn's health. Not only the delivery services, but the records from hospitals nationwide shows that the antenatal and postnatal services are also not being utilized by the women.<sup>4</sup>

The World Health Organization recommends at least 4 ANC visits during pregnancy.<sup>5</sup> Lack of antenatal care and delivery care possesses risk to both the mother and the baby. Antenatal care is vital for the identification and management of pregnancy related health problems. ANC visits also increases the chances of the mother to get safe deliveries with skilled health care professionals.<sup>6</sup>

Of the total number of maternal deaths, 24 percent occur during or after childbirth and 19 percent in the postnatal period. Now when delivery care and postnatal care has been compromised due to the lockdown, these figures are likely to increase.<sup>7</sup>

Previous data in a study suggests that Ebola outbreak in 2014-15 had led to decrease in the maternal admissions, institutional deliveries which were on ascending trend before epidemic. The number of women taking antenatal care and the immunization levels also decreased significantly. This resulted in a 34 per cent increase in maternal mortality (MMR) and 24 per cent increase infant mortality (IMR). The number of maternal deaths, neonatal deaths and still births which were indirectly caused by the epidemic exceeded the direct epidemic related

death.<sup>7,8,9</sup>

This study aims to provide data on the usage of maternal health care services on following domains 1) Antenatal care visits 2) Rate of institutional deliveries (Normal Vaginal delivery and Lower Cesarean Section) 3) immunization services 4) Family Planning Services before and during Covid-19 lockdown in Nepal.

Increased risk and relapse to disease is a common threat to pregnancy as seen with several infections.<sup>10,11</sup> Pregnant female also have increased risk of morbidity and mortality with different infections.<sup>12,13</sup> Even benign maternal infections can results in severe consequences to both the mother and child and some infections leading to various congenital malformations. The new emerging vaccines and treatment can also be contraindicated in pregnancy which can be a major hindrance to treatment and prevention of new emerging infections in pregnant females.<sup>14</sup>

Thus, regular antenatal care is a primary factor to prevent various hazards associated with new emerging infections and risk of maternal to fetus transmission. The risk of lockdown and fear of infection to new outbreak of COVID 19 possess a big burden on the maternal health care system along with various family planning services given by hospitals.

This research aims to determine effect of COVID 19 on maternal visits and care taken by pregnant females, vaccination usage during the lockdown as well as family planning services used. The major purpose of this research is to address the dire situations on maternal health during pandemics. In order to reduce the upcoming issue of risk on maternal and fetal health, family planning and vaccinations, this

study will a approach to policy makers and public health experts to closely work and prevent any decline in the availability of health services to females.

## II. METHODOLOGY

### 2.1 Design

We conducted retrospective observational study to assess the trend of maternal health care services utilization before and during COVID19 lockdown using routinely reported programme data with total duration of one fiscal year. Quantitative method was approached as the study involved collection of quantitative data from existing data source of hospitals of Damak providing safe motherhood services.

### 2.2 Setting

This study was done in Damak. It is one of the oldest municipalities in Jhapa District in Province no.1 of Nepal (figure 1) . It is situated between the Ratuwa River in the east and the Maawa River in the west. Mahendra Highway (longest highway of Nepal) crosses this municipality nearly bisecting it. It is the largest city in Jhapa District as well as in Mechi zone with a population of 75,743 in 2011 A.D. There are total 7 hospitals in Damak. Study was done in 4 hospitals Amda hospital, Lifeline hospital, Damak hospital and OM Mechi hospital.



**FIGURE 1: Study done in Damak, Jhapa district Nepal**

### 2.3 Data collection:

Data was collected from database of four hospitals providing safe motherhood services of Damak from the start of fiscal year 2019/20 (july 14,2019 to june 14,2020). Data were entered into a dedicated Microsoft Excel database and analyzed using SPSS. Data were also cross validated from respective hospitals in Damak. Data was collected Study population included all women seeking maternal health

service which includes antenatal checkup, family planning visit, normal or cesarean deliveries in all government and private hospitals in Damak. Patient seeking other medical services besides maternity health care service are excluded in this study. Descriptive statistics (frequency, percentage) was used to analyze the data. Trend analysis was done to see the changes that have occurred due to Covid-19 lockdown.

## 2.4 Ethical issues and considerations regarding human participants

This research is done from data retrieved from a Hospitals of Damak Municipality, Jhapa and does not involve human participants. Ethical clearance will be obtained from IRC, Nobel Collge. Data was retrieved after taking formal permission from the municipality office.

## III. RESULTS

This section deals with the analysis and interpretation of data collected from four hospitals of Damak providing safe motherhood services. Among the four hospitals, one hospital does not provide immunization service. The data was collected from Shrawan-2076 till Jestha 2077 (July 14, 2019- June14, 2020). The date according to Nepali Calendar and English calendar has been mentioned in the data.

### 3.1 Section 1

The average number of maternal health care services (ANC visits, institutional deliveris, family planning services and immunization ) utilized from the fiscal year Shrawan-2076 till Jestha 2077 (July 14, 2019- June 14, 2020).

**TABLE 1**  
**THE AVERAGE NUMBER OF MATERNAL HEALTH CARE SERVICES**

	Before covid-19 lockdown ((July 17,2019- March 13,2020)		During covid-19 lockdown (March 14,2020- june 14,2020)	
	Mean	Std. Deviation	Mean	Std. Deviation
ANC	2364.1818	689.00970	1377.3333	311.13555
Normal Delivery	363.8182	114.67852	211.6667	64.08068
Caesarean Section	657.2727	175.74532	430.0000	167.68721
Permanent family planing	18.6364	4.80151	18.3333	2.08167
Temporary family planing	11.0000	4.56070	6.3333	4.04145
Immunization	188.2727	99.14241	141.3333	125.12927
TD	151.6364	41.21474	96.3333	21.82506
IUCD	17.3636	14.45180	1.3333	1.52753
Maternal health care services	3772.1818	1014.81484	2282.6667	322.40089

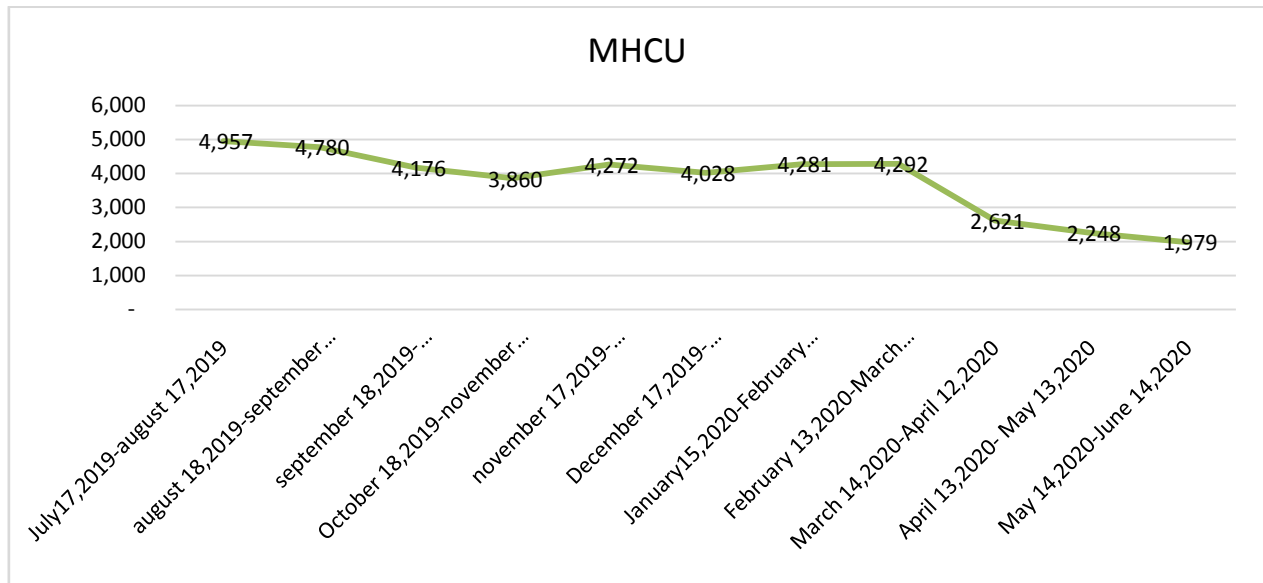
The table 1 shows that the utilization of overall maternal health care services has been reduced during the lockdown period (mean of 3772 before lockdown and 2282 during lockdown).

The utilization of ANC services was reduced during the lockdown period (mean-1377 during lockdown as compared to a mean of 2364 before lockdown). Institutional deliveries (Normal Delivery and Caesarean Section) have also been reduced during the lockdown period. There has been no reduction in utilization of permanent family planning services but the utilization of temporary family planning services has been reduced. Immunization has also been reduced during the lockdown period.

### 3.2 Section 2

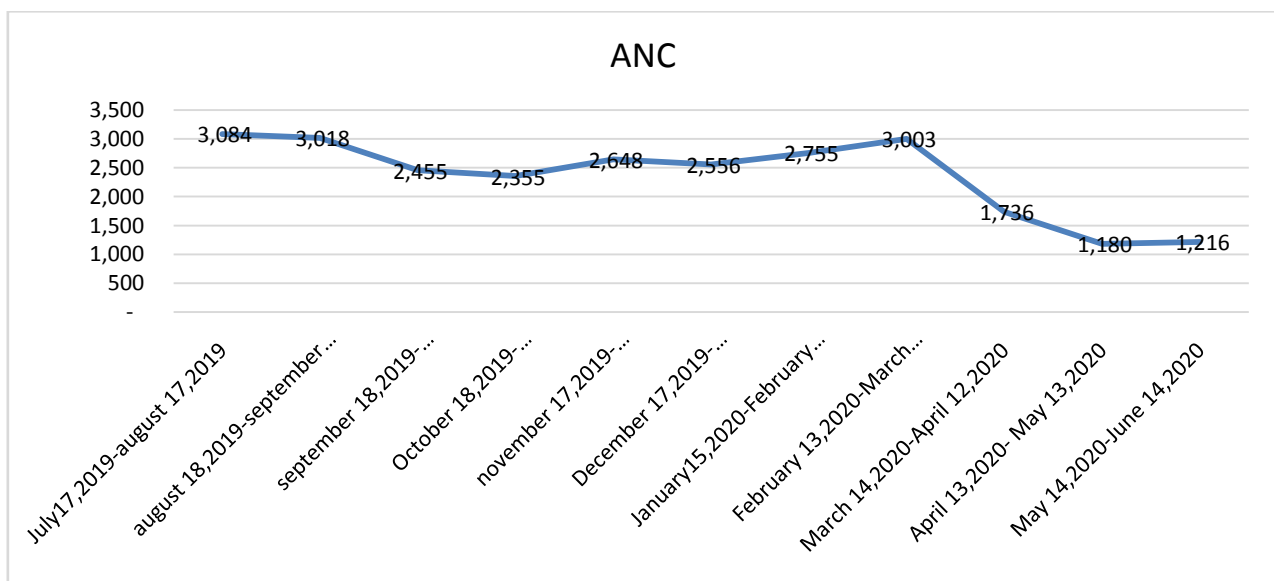
Trend of maternal health care services utilization.

**FIGURE 2: Maternal health care service utilization.**



The figure 2 shows that the overall utilization of maternal health care services has a declining trend since the beginning of Lockdown (march 14, 2020).

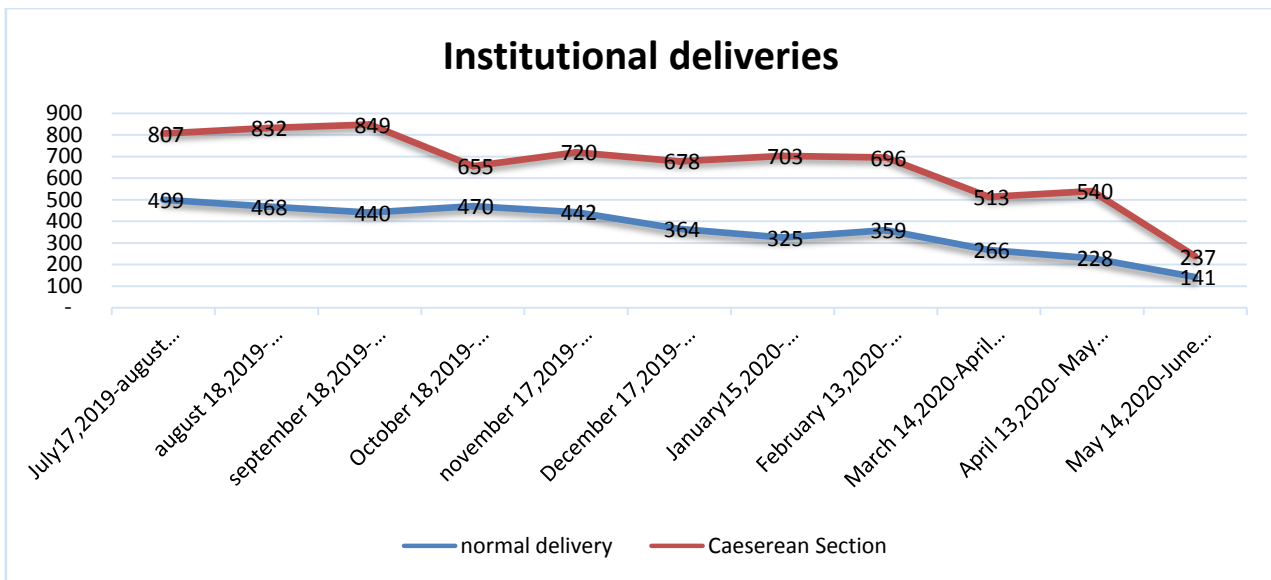
**FIGURE 3: Antenatal care utilization**



The figure 3 shows the change in ANC services utilization. It shows that the number of women visiting hospitals for antenatal care drastically reduced in the month when the lockdown began and continued to

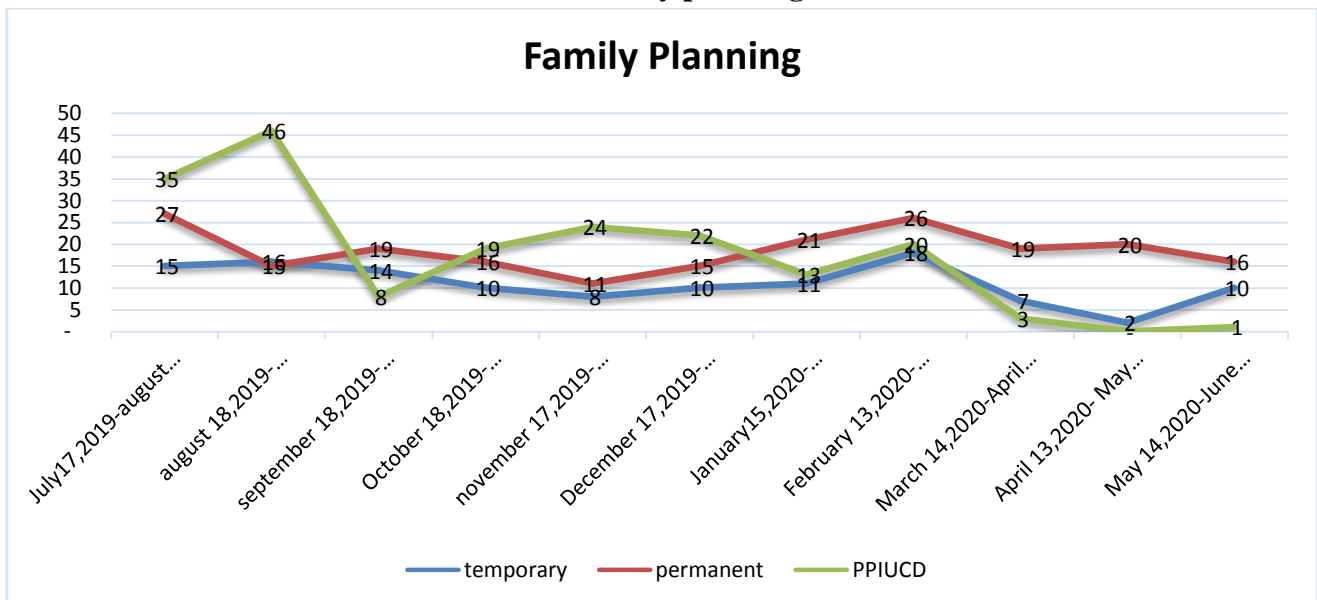
decline in Bhaishak (April 13, 2020- may 13, 2020). It shows a slight increment in the ANC service utilization in the month of jetha (May 14, 2020-June14, 2020).

**FIGURE 4: Number of institutional deliveries.**



The figure 4 shows the number of institutional deliveries from the start of Fiscal year 2076/77 (July 17, 2019). The number of Normal deliveries has a declining trend since the beginning of Lockdown. The number of Caeserean Section declined in the month of Chaitra (March 14-April 14) (beginning of Lockdown) and slightly increased in Bhaishak (April 13, 2020-May 13,2020), but reduced again in the month of Jetha (May 14,2020- June 14,2020).

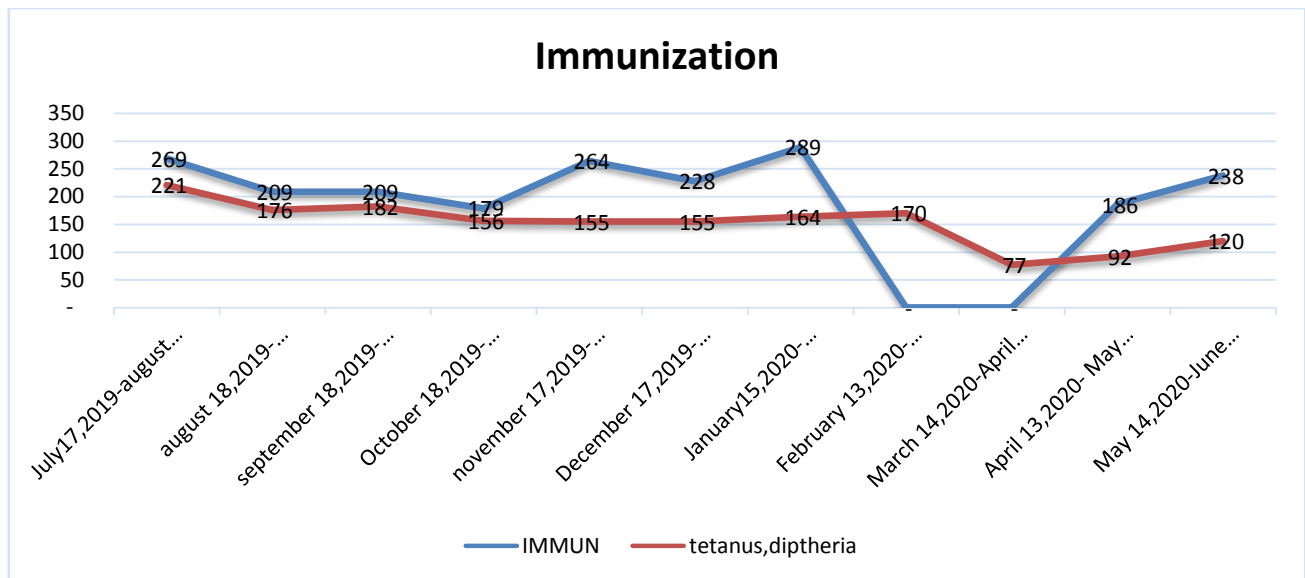
**FIGURE 5: Number of family planning methods utilized**



The figure 5 shows that the utilization of temporary family planning services reduced when lockdown started and is increased in the later month of Lockdown (May 14,2020- June 14,2020) The number of permanent family planning service used reduced when lockdown started (, increased very slightly in the

second month of Lockdown (April 13-May 13) and declined again in the month of May-June. The number of PPIUCD also has a declining trend.

**FIGURE 6: Immunization service utilization**



The trend in immunization shows that there was no immunization done from February 13, 2020 till April 12, 2020, but has an increasing trend in the second and third month of Lockdown. The number of TD vaccination decreased in the month of Chaitra (March 14, 2020- April 12, 2020) but has an increasing trend in the month of later months of lockdown (April 13, 2020- June 14, 2020).

#### IV. DISCUSSION

This study provides evidence of declining maternal health facilities utilization after nationwide lockdown due to COVID 19 outbreak. Antenatal care visits has been reduced to half. Cesarean and normal delivery, immunization and family planning follow decreasing trend. *The Lancet Global Health*, Timothy Robertson and colleagues report the indirect effect of COVID19 on maternal and child mortality using Lived Saved tools (LiST). They have created 3 scenarios in which they have showed different number of reduction in 4 component (availability of health worker, availability of supplies and equipment, demand of health service and access of health services) over period of 3, 6, 12 months. They estimated that with when there is a reduction of 39.3–51.9% and wasting increase up to 50% it will result in 56700 additional maternal death and 1157000 additional child death over 6 month period. This result would represent 9.8–44.7% increase in under-5 child deaths per month, and an 8.3–38.6% increase in maternal deaths per month.<sup>15</sup> This study gives awareness about how disruption in maternal health service can increase the death count. From our study which shows decline in overall utilization of maternal health but it does not show cause of decline whether it is due to decrease in supply or demand of health services. But overall decline in maternal health services can have a serious impact on additional maternal and child death. Therefore Government should allocate health resources and manpower to intervention which can make a huge impact on ongoing crisis. Parental administration of uterotonics, antibiotics and anticonvulsant and clean birth environment would prevent death of 60% additional maternal death.<sup>15</sup>

## V. CONCLUSION

Since the beginning of Lockdown, the utilization of ANC services, institutional deliveries has been on a declining trend. The utilization of temporary family planning services has shown an increasing trend on the month of Jestha (May 14, 2020- June 14,2020), whereas permanent family planning method has a declining trend. Immunization services, though was completely unused when COVID-19 began, has shown an increasing trend on the later months of Lockdown.

## DISCLOSURE OF INTEREST

Since this study is self funded and no organization is involved, there is no disclosure of interest.

## CONTRIBUTION TO AUTHORSHIP:

**Sandhya Budhathoki:** conceptualization, methodology, analysis **Bibhuti Adhikari:** original draft preparation, data collection, **Rupesh Ramtel:** writing, reviewing, editing.

## ETHICAL APPROVAL

This study was approved by IRC of Nobel College.

Reference number: FNIRC307/2020.

Date: 05/06/2020.

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# Perceived Economic Crisis due to COVID-19 and its Impact on Health

Sandhya Budhathoki<sup>1\*</sup>, Puspa Kumari Deo<sup>2</sup>, Bibhav Adhikari<sup>3</sup>

<sup>\*1,2</sup>Lecturer in Nursing, Nobel College, Sinamangal Rd, Kathmandu 44600, Nepal

<sup>3</sup>Associate Professor in Biostatistics, LA College of Health Sciences, Sinamangal, Kathmandu 44600, Nepal

**Abstract**— A mixed research design was adopted to explore the perceived economic impact of COVID-19 and its impact on health. Quantitative data was used to find out the status of microeconomic parameters and FGD was done to find out the perceived economic impact and its impact on health. The quantitative data was retrieved from the Nepal Rastriya Bank's database. FGD was conducted among experts in the field of economics and health. The quantitative analysis showed decline in remittance and economic growth. The thematic analysis of the FGD revealed that remittance will decrease further and will have a negative economic growth. The participants predicted that the population falling under poverty line will also increase. They also predicted that mental health problems like depression, anxiety, PTSD, substance and alcohol use and sleep problems are likely to increase. They also predicted that the after effects of this pandemic will bring a huge burden on public health and the non-communicable disease is likely to increase. This study recommends that employment opportunities needs to be created and the health service points need to be strengthened. Mental health assessment should be made a part of health assessment in quarantine. This study emphasizes on maintaining physical distance while being socially connected.

**Keywords**— Covid-19, Economic Crisis, FDP, Economy in Covid-19.

## I. INTRODUCTION

Pneumonia of unknown cause detected in Wuhan, China was first reported to the WHO Country Office in China on 31 December 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 11 February 2020, WHO announced a name for the new coronavirus disease: COVID-19.<sup>1</sup>

COVID-19 has emerged as a global health emergency. It has not spared any continent, the exception of Antarctica. As of 27<sup>th</sup> May, 2020, the cases of COVID-19 has been recorded as 5 488 825 cases (84 314) globally with 349 095 deaths (5 581) (WHO, 2020). Worldometer has reported a total case of 886 with 5 deaths as of 27<sup>th</sup> May 2020 in Nepal.<sup>1</sup>

Very country it touches, it has the potential to create devastating social, economic and political crises that will leave deep scars. This crisis will have a direct and indirect impact on health as well. The International Labour Organization estimates that 195 million jobs could be lost.

The Economic Times: India Times (28 May, 2020) has reported that Some 122 million Indians were forced out of jobs last month alone, according to estimates from the CMIE. Daily wage workers and those employed by small businesses have taken the worst hit. These include hawkers, roadside vendors, workers employed in the construction industry and many others.<sup>4</sup>

According to the economic survey 2076-2077 (2019-2020) of Nepal, the international monetary fund has estimated that there will be shrinkage of 3% in the world economy in 2020. The survey has

mentioned that the economic growth of Nepal estimated to be 2.3% as compared to 7.3% in the last three years.<sup>2</sup>

The estimated poverty headcount ratio (at the \$1.90 per person per day international poverty line) was 15 percent in 2010 in Nepal, which further declined to 8 percent in 2019. At a higher line of \$3.20 a day, 39 percent of the population in Nepal is estimated to be poor in 2019, a 15 percentage-point decrease from 2010. About 31.2 percent of the population that is estimated to live between \$1.9 and \$3.2 a day face significant risks of falling into extreme poverty, primarily because of reduced remittances, foregone earnings of potential migrants, job losses in the informal sector, and rising prices for essential commodities as a result of COVID-19.<sup>5</sup>

Several studies support the fact that financial depressions have a direct impact on the overall health, on the public spending directed to the health care system, on the quality of the provided services and the restructuring the roles and functions of the health care personnel. The downturns in economic activity increase the rates of unemployment which consequently affect mental and physical health.

The Asian economic recession of 2008, which caused a sudden increase in unemployment, has also led to an increase in suicide mortality rates, reflecting a significant harmful mental health effect associated with the recession. As described by (Economou, 2008) in a workshop that was held in 13 European Union countries, there is a strong relationship between unemployment and an increase in cardiovascular mortality. One possible explanation is that acute stress and depression have been associated with elevated levels of cytokines and leukocyte which lead to elevated blood pressure via catecholamines.<sup>3</sup>

We know that the level of anxiety rose significantly when the SARS outbreak occurred. For example, in Hong Kong, about 70% of people expressed anxiety about getting SARS and people reported they believed they were more likely to contract SARS than the common cold.

Global Economic Effects of COVID-19 Congressional Research Service 5 global financial crisis, the IMF estimated that the global economy could decline by 3.0% in 2020, before growing by 5.8% in 2021; global trade is projected to fall in 2020 by 11.0% and oil prices are projected to fall by 42%. The economic effects of the pandemic are being spread through three trade channels: (1) directly through supply chains as reduced economic activity is spread from intermediate goods producers to finished goods producers; (2) as a result of a drop overall in economic activity, which reduces demand for goods in general, including imports; and (3) through reduced trade with commodity exporters that supply producers, which, in turn, reduces their imports and negatively affects trade and economic activity of exporters.

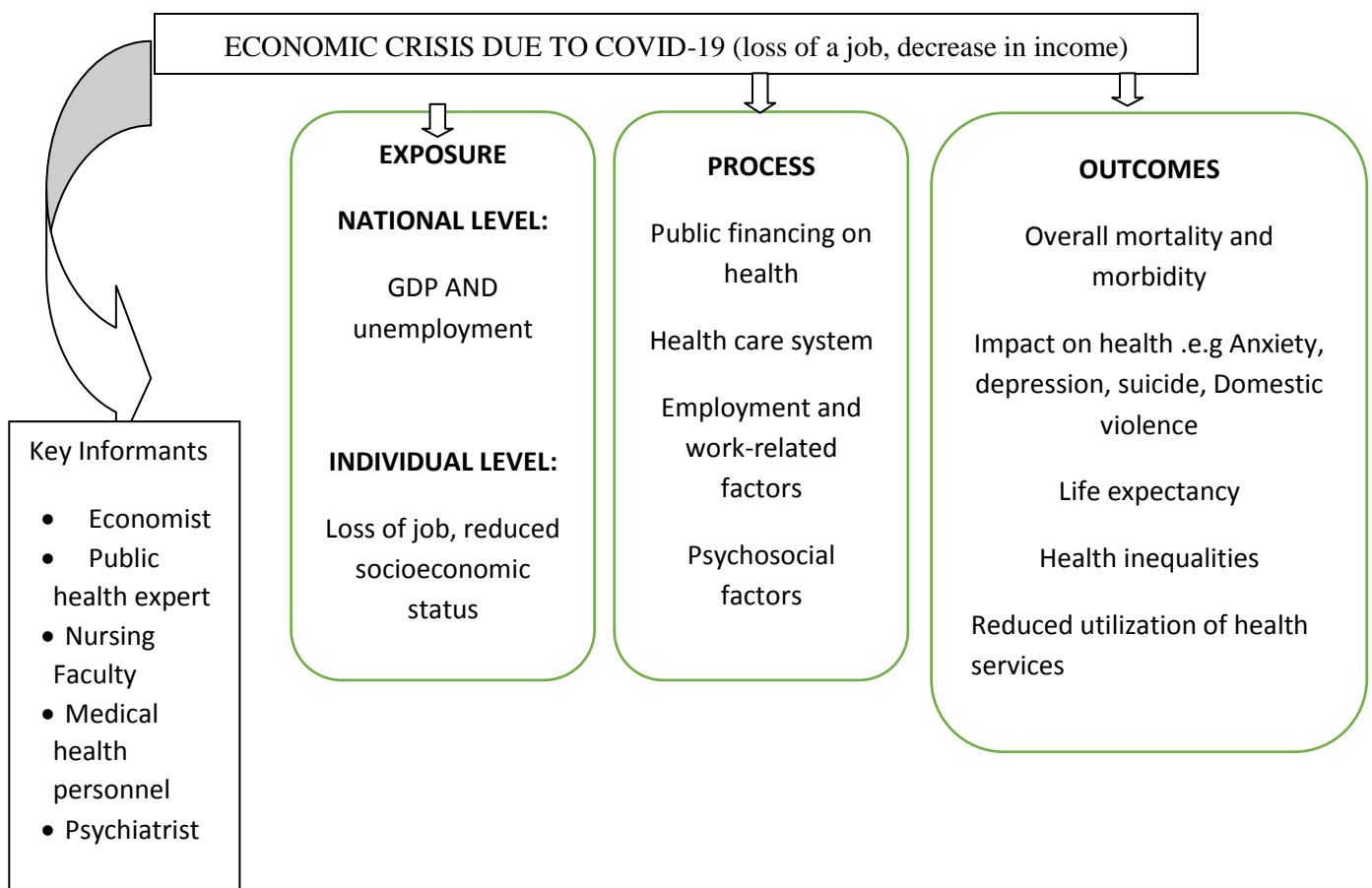
- The economic impact of coronavirus is a rising strain across the world.
- A new survey found respondents in Vietnam, China, India and Italy expect to take the greatest personal financial impact.
- The perceived threat to health increases in proximity to hotspots.
- The Ipsos poll of 10,000 adults in 12 countries, conducted 12-14 March, suggests rising anxiety about personal financial exposure, including employment. The perception of threat to health increases with proximity to hotspots, despite social distancing measures and travel bans in place across large areas of the world.

The COVID19 Pandemic has brought several alarming risk factors such as social isolation, anxiety and depression, inadequate treatment and availability and poor seasonal timing as reported by JAMA psychiatry (2020). There is evidence that during the 1918-19 influenza pandemic there was an increase in the number of suicide deaths in the USA. And among Hong kong elders during severe acute respiratory syndrome (SARS) epidemic in 2003. (Cheung et al, 2008).

It has been projected that in 2020, suicide accounts for one death every 20 seconds, and the large majority of those occur in low and middle-income countries (WHO, 2016).The stressors caused by the pandemic are sure to exacerbate the suicide rate worldwide.

In Nepal, almost 15 people committed suicide everyday with a total of 5317 persons killing themselves in 2017/2018. During the lockdown period from March 24 to May 2 this year, a total of 492 people committed suicide.

### CONCEPTUAL FRAMEWORK



## II. OBJECTIVES OF THE STUDY:

### 2.1 General objectives:

To explore the perceived economic crisis and its impact on health.

### 2.2 Specific objectives

To compare the different economical parameters before and during the COVID-19 pandemic.

To determine the perceived economical impact of COVID-19.

To explore the perceived health impact due to the economic crisis on health from the experts working on health (public health expert, nursing experts and psychiatrists)

### **2.3 Research questions**

- What is the status of the macroeconomic parameters of FY 2076/77? (will be quantitatively analyzed).
- What can be the perceived impact of Covid-19 on economy of Nepal? (will be qualitatively analyzed).
- How will the changes in economy affect on the health sector of Nepal? (will be qualitatively analyzed).

**Remittance:** Remittance inflows decreased by 0.5% to Rs. 875.03 billion in the review period. It had increased by 16.5% in the same period of the previous year.

## **III. MATERIALS AND METHODS**

### **3.1 Study designs**

Mixed method design was used to explore the perceived economic crisis and its impact on health.. Quantitative study was done to find out the changes in economical parameters. A qualitative approach was most appropriate to explore the perceived economic crisis due to COVID-19 and its impact on health as we can get in-depth information from the experts working in the field of economics and health. Also, the information that this study explores is more analytical and the use of quantitative tools might narrow the exploration of information.

The populations of the study will were experts working in the field of economics and health.

#### **3.1.1 The requirement of Respondents and Sample Size**

Experts (atleast 5 years of work experience in their respective field) working in the field of economics and health were eligible to participate in the study. Creswell (2007) suggest 4-8 participants for focus group discussion. However, the authors believe that these are only rules of thumb. So for this study 2 economist, 1 psychiatrist, 1 physician, 2 public health experts and 2 nursing professionals and 1 nutritionist were invited for focus group discussion. Participants were selected using a purposive sampling technique.

#### **3.1.2 Philosophical Paradigm**

This was an ontological study. An interpretative approach was applied to get in the base of knowledge.

#### **3.1.3 Inclusion criteria**

The inclusion criteria for the participants was atleast 5 years of experience in the respective field of economics and health. And those who were willing to participate.

#### **3.1.4 Study variables**

Perceived economic impact and its impact on health.

### **3.2 Data collection tools**

The data on economical parameters was retrieved from published source (macroeconomic report based on the 12 months data of FY 2076/77) from Nepal Rastriya Bank. The unstructured interview guide was developed in such a way that it ensured coherence in the study approach and gives the interview sessions a general direction concerning the topic raised and discussed.

### **3.3 Data collection procedures**

Quantitative data regarding economic parameters was obtained from report published by NRB.

### **3.4 Qualitative data collection procedure:**

Informed consent was taken from the respondents via email. A Focused Group Discussion was conducted using Zoom Meetings. FGD was conducted in two sessions; one with the experts in the field of economics and other with the experts from the field of health (psychiatrist, public health expert, nursing academician and a nutritionist). FGD was used as the measure to collect data because they provide opportunities to explore issues deeper. And time for the Focus group discussion was 1hour. Data was collected based on the question and objectives. FGDs are interactive thereby providing room to clarify the issues and encourage discussions during the interview.

The session was recorded with consent from the respondents. The discussion was continued until the information reached saturation based on the study questions.

Pretest was conducted before initiation of real study. After that modified the questionnaire if needed.

### **3.5 Data analysis**

The quantitative analysis was done through the secondary data of economic parameter.

For qualitative study, thematic analysis was used to analyze the perceived economic impact and its impact on health.

Firstly, information was extracted from the recording system and all the transcribed data was coded with the printed document with the help of underlined by researcher. Underlined words and sentences were rechecked by other researcher and confirmed the final one code. Coding was done with the rigorously and carefully integrated into both examination and interpretation of data. Themes of the events were analyzed and were developed based on the coding. All the transcripts was read and highlighted line by line and word by word which produced important message.

Secondly, after finding out the underline keywords, appropriate name was given or code to symbolize it. Code was written in the right hand side of the transcript after identify the highlighted key words. Code name was produced through the participant's information. Common codes were interconnected with the other transcription, which was compared and contrast with the analysis. After reading the transcript, research members were made consensus on extracting the significant keywords and code.

Thirdly, all the statements and developed meanings were checked by other expert who confirmed the method to be accurate and consistent.

### 3.6 Ethical Considerations

Ethical clearance was obtained from Nobel College, Kathmandu. Informed written consent was taken from the respondents. Confidentiality was maintained. Recording was done with consent from the respondents and the records were deleted after the analysis.

All the key informants were informed before start the zoom meeting interview with the objectives of the study. The entire interview was kept anonymous and confidential. Privacy and right to withdrawal was granted to all the key informants. No any incentive was given to the participants.

### 3.7 Trustworthiness of the study findings

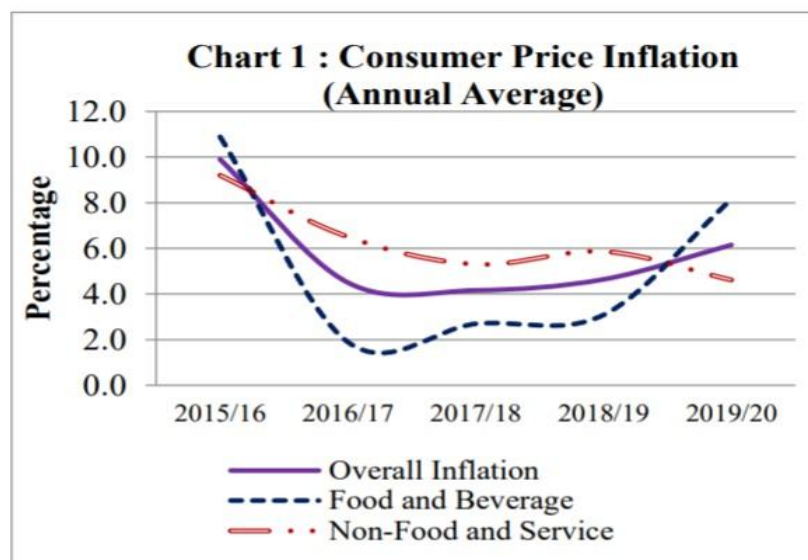
Validity and reliability of the qualitative research was maintained with the strength of the data collection, data analysis and descriptions. Trustworthiness was maintained throughout the study process. Pretest increased the credibility of the study. Validity was maintained by experts and the ideas and theme was developed independently and thorough discussion with the research member. All the translation and transcripts was doubled checked by a bilingual translator who is expert in English and Nepali. Coding process, analysis and descriptions was checked by other experts.

## IV. RESULT

### 4.1 Quantitative analysis of the macroeconomic status.

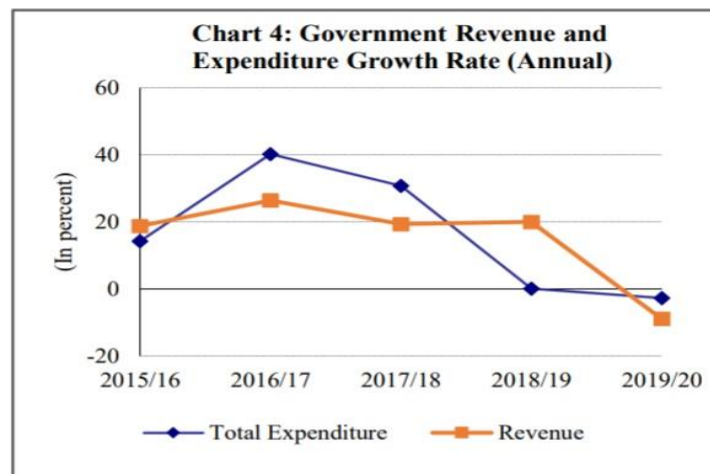
The macroeconomic status of Nepal has been published by the central bank based on 12 months data of the fiscal year 2076/77 (april 2019-15<sup>th</sup> july 2020). Some of the major highlights of the reports are:

**FIGURE 1: Inflation.**



The y-o-y consumer price inflation stood at 4.78% in mid-July 2020 compared to 6.02% a year ago. Food and beverage inflation stood at 8.16% whereas non-food and service inflation stood at 3.09% in the review month.

**Remittance:** Remittance inflows decreased by 0.5% to Rs. 875.03 billion in the review period. It had increased by 16.5% in the same period of the previous year.

**FIGURE 2: Government revenue and growth rate.**

**Government expenditure:** Total expenditure of the federal government based on banking transactions (excluding direct payments and unrealized cheques) stood at Rs. 1094.34 billion.

**Government revenue:** It decreased to Rs. 793.78 billion which was Rs. 871.78 billion in the corresponding period the previous year.

## 4.2 Qualitative analysis of the perceived economic crisis and its impact on health

### 4.2.1 Economy of Nepal

All of the participants said that the unemployment rate will increase in Nepal since there will be return back of Nepali from abroad. All the participants said that there will be shrinkage in remittance will bear a negative trend.

One of the participants said “Even if the impact on remittance is not seen today, there will be a huge impact in the coming future. Remittance might shrink by 20%”.

All of the participants said that there will be a negative economic growth and the GDP will decline.

One of the participants said “Remittance contributes to 25% of the GDP, agriculture 25%, consumer and retail contributes 14% of GDP, tourism 6%, aviation 3%, and construction 7%. Since all of these sectors are affected by COVID-19, there will be an obvious decline in the GDP.”

Another participant said that “The world is expecting an economic recession more than ever seen or heard of”.

### 4.2.2 Poverty and quality of life

All of the participants said that the percentage of population falling under poverty line will increase due the effect of COVID-19.

One of the participants said “1.17% of the population was expected to fall below the poverty line even after 2.3% of economic growth. Now when we are expecting 0% economic growth, 21% of the population will fall below poverty (18.6% were under poverty before COVID-19. If the economic growth becomes negative, this figure will increase further.”

Most of the participants said that because of the reduced economic growth and job less, the quality of life of people will degrade.



### 4.2.3 Effect in health

All of the experts on economics said that the expenditure on health will decrease.

One of them said “Now when income has reduced due to COVID-19, the expenditure in health also decreases, which means that people seeking private health services will go to government hospitals. So the pressure in government and community hospitals will increase.”

Experts on mental health said that Depression, anxiety, OCD, alcohol and substance abuse, PTSD, sleep problems are the main mental health effects of COVID-19.

Expert on nutrition stated that people do not have access to a balanced diet because of food scarcity and because farmers are not able to take the produced food to the market. The participant further mentioned that “People are consuming calorie-dense food instead of nutrition dense food. This will also bring health hazard among the population.”

Expert on public health said that COVID-19 has an iceberg phenomenon, being tested positive for COVID-19 is the tip of iceberg, while other effects are the submerged part. The participant further stated that “These effects can be mental health problems, but the most alarming is the increase in non-communicable disease.”

### 4.2.4 Addressing increasing inequalities

All of the participants believed that employment opportunities must be created.

One of the participants said that “resources should be distributed equally to all the sectors like agriculture, health, industries etc”

Another participant said “the transfer is the main strategy to address the inequality. i.e. take a little more from rich and give a little more to the poor”.

Another participant said “income level should be increased, for which skill should be increased, for which education sector should be strengthened.”

### 4.2.5 Equipping future society for health emergencies

Most of the participants said that the health care system of the country should be strengthened. Health care staffs should be given training.

One of the participants said that “there should be a separate budget allocated for nutrition. Agriculture technicians and biofertilizers should be made available.”

Drawing attention to mental health, the participants said that physical and mental health screening of the people in quarantine should be done and a mental health help desk with a focal person should be established in every hospital.

One of the participants emphasized on teaching people to live with COVID-19 rather than being scared of it and further added that “People should be connected socially more than ever during this pandemic but physical distancing is what should be maintained.”

## V. CONCLUSION:

COVID-19 has brought about a lot of changes in the economy of the nation, besides health. This negative change in economic status has further brought more health related effects. This study was

conducted to find the perceived economic impact due to COVID-19 and its effect on health. the results showed that there is a decline in GDP and remittance and will have an increment in poverty rate. This in turn will have an effect in health, in terms of increase in mental health problems and non communicable diseases. There will be a spike in nutritional related health issues also. This study further recommends that the health service point should be strengthened, mental health assessment and support should be made widely available. This study emphasize on physical distancing while being socially connected.

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# Physical Therapy A Critical Component in Breast Cancer and Secondary Lymphedema: A Rehabilitation Perspective

Dr. Ashraf Thoker

Specialist Physiotherapist Neurological Disorders Department of Physical Therapy AMI Hospitals Ministry of Interiors KSA

## **Abstract—**

**Purpose:** *The main purpose of the methodical review is to obtain the importance of Physiotherapy Rehabilitation in breast cancer-related lymphedema in order to elucidate the role of Physiotherapy in these patients.*

**Methods:** *A systematic data search was performed using Google scholar, PubMed (from February 2001 till August 2020) and is focused on the rehabilitative aspect of breast cancer related secondary lymphedema and undertaken according to the PRISMA statement with Levels of Evidence (LoE) assessed.*

**Results:** *14 randomized controlled trials that included 158 women with breast cancer in after care were included. The included for articles studies of effect different types of physiotherapy regimens like exercises that consisted of lymph training, swimming, resistance exercise, gravity-resistive exercise and aerobic exercises. The mentioned articles were thoroughly analyzed and included in the review.*

**Conclusion:** *The evidence indicates that Physiotherapy can improve subjective and objective parameters in BCRL patients although it is found to be helpful in improving the quality of life of these patients.*

**Keywords—** *Breast cancer, Lymphedema, Physiotherapy, Rehabilitation.*

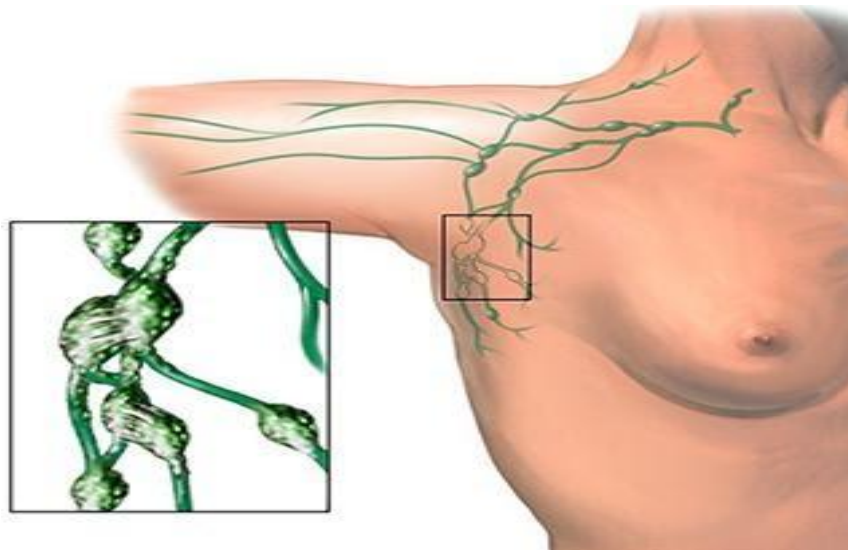
## I. INTRODUCTION

As per the recent data breast cancer is most common cancer in women worldwide. There is been satisfactory improvements in early detection, diagnosis, treatment and reduction of complications, side effects which includes fatigue, weakness, loss of muscle extensibility, limited shoulder range of motion, upper-body pain, pulmonary complications, neuropathy, decreases in lean mass and concomitant increases in fat mass,. The BCRL arises as a result of fluid accumulation in the interstitial tissue due to damage of the lymphatic system, induced by surgery and/or radiation, or tumor-induced neo-lymph angiogenesis. Maximum proportion of women undergoing axillary intervention develops swelling upto 2 years. Chances of breast cancer related lymphedema is further increased by some risk factors like extensive surgery, obesity, axillary lymph node procedure, and radiotherapy to the regional lymph nodes. Patients with BCRL typically suffer from a swollen upper limb, with concomitant feelings of weakness, heaviness, discomfort, and pain. Furthermore, there is an increased risk of infection and a chronic, progressive course of disease, leading to psychosocial distress and impaired quality of life (QoL). Treatment of BCRL typically consists of a multimodal therapy approach, including complex decongestive medicine, physiotherapy, and skin care. Although previous studies have indicated numerous positive benefits of exercise in breast cancer treatment such as improvements in physical performance, body composition, and quality of life along with an acute and chronic reduction in fatigue. The lack of recommendation to exercise rehabilitation along with the symptoms of breast cancer related

lymphedema often leads to insecurity of patients and physical activity avoidance. The vicious cycle resulted in which sedentary subjects leading to increase in body mass and to an undesired progression of the disease because overweight and obesity risk factors for the development of lymphedema. Therefore, the American Cancer Society recommends that primary care clinicians should counsel survivors on how to prevent or reduce the risk of BCRL, including weight loss for obese and overweight and to adopt an individual tailored exercise program. A number of studies have been published that have investigated the effect of exercise on BCRL and, as a result, the effects of resistance exercise on BCRL have already been extensively reviewed. However, to the best of our knowledge, previous reviews have not concluded the effect of physiotherapy on BCRL and hence there is a need to know whether the physiotherapy rehabilitation is found to have some positive effects on BCRL or not.

## II. MATERIAL AND METHODS:

A systematic PubMed search was conducted in January 2019, and studies were considered from February 2001. Key words searched included ‘breast cancer-related lymphedema or lymphedemas effects of physiotherapy on Breast cancer related lymphedema. Other terms used were ‘physical activity’, ‘physical exercise’, ‘breast cancer’, ‘prevention’, ‘physical fitness’, ‘exercise program’, strength training sports therapy and endurance exercises, resistance training ‘exercise intervention’. Women suffering from BCRL had to be involved in an interventional physical activity. The intervention had to involve a form of physical activity for women who are already suffering from BCRL. Studies that had a preventive approach or that included both women with BCRL and women those were at risk for BCRL were excluded from the study.



**FIGURE 1**

**TABLE 1**

**INVOLVED CRITERIA IN THE STUDY**

Inclusion criteria	Exclusion criteria
Breast cancer diagnosis	Preventive therapy or mixed approach Diagnosis
BCRL diagnosis	Studies published before 2000

## 2.1 Randomised controlled studies Women

This review focused on outcome measures that presented the role and importance of physiotherapy on Lymphedema and it focuses on the cases of BCRL. The review was aligned to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) process.

## 2.2 Evidence criteria levels

I: Meta-analyses of RCTs

IA: RCT of breast cancer survivors

IB: RCT based on cancer survivors across

## 2.3 Multiple cancer sites

IC: RCT based on general population experiencing a specific longterm or late effect (e.g., managing menopausal symptoms, sexual dysfunction, etc.)

IIA: Non-RCTs based on breast cancer survivors

IIB: Non-RCTs based on cancer survivors across multiple sites

IIC: Non-RCTs for general population experiencing a specific long-term or late effect

III: Case–control study or prospective cohort Study

0: Expert opinion

## III. RESULTS:

Number of 38 studies were identified and filtered by “clinical trial,” and “female.” Following this, 25 studies were excluded and 14 were selected for abstract- or full-text-analysis. From these, 14 articles included in this review that comprised a total number of 158 patients. The studies were published between 2001 and 2020 and the study sample sizes ranged from 14 to 151 patients. All women included in the trials had been diagnosed with Breast Cancer Related Lymphedema at study entry and had completed the primary therapy for breast cancer. The average age of the women was 55 years, and the intervention period ranged from 6 weeks up to 1 year. The number of training sessions varied between one and seven sessions per week. All interventions were at least initially supervised. Measurements in all trials were undertaken at baseline and at different times during and after the interventions. Arm volume and arm circumference were assessed used in the studies: limb circumference measurements were undertaken in 6 studies. All included studies had a controlled randomized study design and included women with pre-existing BCRL. Of the 14 studies, only 2 had both the participants and assessors blinded and two studies did not mention any blinding. The summary of the included articles are as follows:

- Schmitz et al. 2010 (20) - RCT - To assess the upper limb girth after rehabilitation in BCRL cases -physiotherapy was found to be effective.
- Robyn C. Box et al. 2002 (15)- RCT - To determine the effects of physiotherapy on post surgery breast cancer Lymphedema -A significant reduction in development of secondary Lymphedema has been concluded.

- Marianne Eurertz et al. 2011 (16) – RCT - To conclude the effect of physiotherapy on Lymphedema as secondary complication of Breast cancer surgery Positive effects of physiotherapy on Lymphedema was concluded.
- Nela Devoogt et al. 2018 (17) - RCT - Effect of physiotherapy on Upper limb volume on post cancer breast surgery Reduction in the girth of the affected limb was concluded.
- Bolette S Rafn et al 2018 (18) Pilot- RCT - Effect of physiotherapy on Lymphedema on Quality of life of the patient Improvement in the Quality of life of the patients.
- Freek T. Baumann et al. 2018 (19) – RCT- Effect of physiotherapy intervention on Upper limb weight on post cancer breast cancer surgery patients. Reduction in the weight of the limb was found.
- Sing B, Buchan, Box R, et al. 2016(3)-RCT-compression use during exercise intervention to determine the effects of physiotherapy in breast cancer – related lymphedema.
- Torres Lacomba et al. 2010 (21) - RCT- Pre and post Surgery effects of physiotherapy on BCRL It limits the lymphedema and hence give positive results.
- Zimmermann et al. 2012 (22) - RCT - Effect of physiotherapy on Upper limb volume on post Cancer breast surgery It reduces the volume and hence found to be beneficial.
- Devoogdt et al. 2011 - RCT - Effect of physiotherapy intervention on Upper limb weight on post cancer breast cancer surgery patients It reduces the upper limb girth.
- Zhang et al. 2016(15) - RCT - Effect of physiotherapy intervention on Upper limb weight on post cancer breast cancer surgery patients It has positive effects post intervention.
- Sinead Cobbe et al. 2017 - RCT - Complex decongestive therapy as a regimen as a part of physiotherapy rehabilitation for lymphedema patients CDT therapy was found to be effective on Lymphedema.
- Maria Torres Lacomba et al.2010 - RCT - Early physiotherapy treatment for pre and post of BCRL Patients Physiotherapy was found to be effective.
- Donald C. McKenzie 2014 - RCT - Effect of progressive upper limb exercise program Progressive upper limb exercise was found to be effective.

#### IV. DISCUSSION

The intervention had to involve a form of physical activity for women who are already suffering from BCRL. Studies that had a preventive approach or that included both women with BCRL and women those were at risk for BCRL were excluded from the study.

To the best of knowledge, this is the first methodical review that has considered the effects of different types of physical exercise as a part of physiotherapy rehabilitation on women suffering from BCRL. Within the 14 included studies, we found all the included studies conclude the positive effect of physiotherapy regimens on BCRL patients. The findings of the present systematic review demonstrate that physical exercise improves BCRL state. To the best of our knowledge, this systematic review is the first to summarize the effects of different types of physical exercises on BCRL and was produced according to the guidelines of PRISMA. We believe this paper provides excellent grounds for

supporting guidelines on the role of exercise in women with BCRL. As the studies summarized in this review were published from 2001 to 2020, the findings are both recent and timely. Nevertheless, when interpreting the present findings one should consider possible limitations. The present study only concludes the conclusion part of the included studies. The study did not critic or discuss the regimens independently. A number of studies might be possible by adding different regimens or interventions for pre or post breast cancer surgery patients. Moreover, as a result of the low number of studies available, no standard definition for BCRL was used and the measurement techniques differed among the studies. However, while this must certainly be considered as a limitation of the present review, it should be noted that there is a lack of definition for BCRL even in medical care, making the investigation of treatment methods challenging. Based on the present findings, it can be concluded from the current literature that physical exercise is not contraindicated for women with BCRL. When completed according to the ACSM guidelines for cancer survivors there is no restriction recommended regarding BCRL and any form of exercise. As such, our findings are in contrast to the early recommendations by health care professionals to avoid vigorous or excessive upper-body exercise, including activities of daily living. Moreover, future studies may also focus on the possible preventive aspects of physical exercise for the development of BCRL in breast cancer patients.

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## Anti Bacterial Action of Piper Cubeba Extract in UTIs

Angad Verma<sup>1\*</sup>, Sangamesh B. Puranik<sup>2</sup>, Rohit Saraswat<sup>3</sup>, Mahesh Kumar Jhajharia<sup>4</sup>,  
Ritu Sharma<sup>5</sup>

School of Pharmacy, OPJS University, Churu, Rajasthan

\*Corresponding Author

**Abstract**— Thirty five *E.coli* isolates were collected from patient suffering from long term urinary tract catheters and urinary tract infection for both genera with age ranging between (11-60) years. The isolates were identified according to cultural, microbiological, biochemical testes. Detection bacteriocin production by *E. coli* was showed only (5) isolates of *E. coli* produced bacteriocin. To esteemed effect of *P. cubeba* fruits extract on bacteriocin production from *E. coli* exposed to this extract, the results showed did not changing in bacteriocin production but the extract caused changes in the antimicrobial activity between bacteriocin produced before and after treated bacteria with *P. cubeba* fruits extract. In the case of bacteria cultured without the extract, protein concentration of partially purified bacteriocin (by ammonium sulphat) was (9.21mg/ml) while bacteriocin protein concentration of bacteria grown with the extract was (10.6mg/ml). The statistical analysis of result did not show significant differences and “p value” was 0.177. SDS PAGE reveal that bacteriocin have molecular weight (25KDa) and identified as Colicin.

**Keywords**— *Escherichia coli*, *Piper cubeba*, *Bacteriocin*, *plant extract*.

### I. INTRODUCTION

Virulent bacteria are capable to create molecules that dynamically reduce the immune response of the host, so increased bacterial persistence and tissue damage. The virulence factors encoding genes of uropathogenic *E. coli* are localized on chromosomal gene clusters called “pathogenicity islands” [1; 2]. Virulence factors have a vital role in determining the invading of organism to the urinary tract and the level of infection. Uropathogenic *E.coli* (UPEC) infect the urinary tract via expressing specific virulence factors that allow adherence and colonization of the lower urinary tract [3; 4]. Bacteriocin is one of these virulence factors which are Proteinaceous toxins that produced via bacteria and have the ability to inhibit the growth of similar or closely related bacterial strain [5]. Bacteriocins, a member of the narrow-spectrum toxins are described as the “microbial weapon of choice”, due to their abundance and diversity among producing bacteria [6]. They are similar to killing factors of yeast and paramecium but are structurally, functionally, and ecologically different. Applications of bacteriocins are tested to evaluate its application as narrow-spectrum antibiotics [5]. They are classified in different ways, such as producing strain, mechanism of resistance, mechanism of killing. There are large classes of bacteriocin that are only phenomenologically related. These classes are the bacteriocins from gram-positive bacteria, colicins, [7] microcins, and the bacteriocins from Archaea [8]. *E. coli* produce two kind of bacteriocins, classified in dependent on their molecular weight into colicins (25-80 kDa) and microcins (10 kDa). Colicins and microcins are alike in numerous ways, but microcin synthesis is not lethal to the producing strain additional, and all colicins are encoded by plasmid, while genes encoding to microcin found on the chromosome [7].

Recently, attention to medicinal plant studies that focusing on inhibition of as a target activity is

increase, several bioassays to assess virulence factors have developed for number of microorganisms, especially bacteria and yeast. This is an important source of molecules to investigate new anti-virulence factors mechanisms of microbes. Many medicinal plant metabolites have antimicrobial activity [9; 10]. Traditional medicine Practitioners think that the components of plants are unique because of them contains both active ingredients and “non active” components that are play a role in enhancing the well being of their patients [11]. Numerous virulence factors can be neutralized via plant compounds. A broad field of studies on this subject is further on science advances in phytochemistry and molecular microbiology providing new features that will end in virulence factors based new therapy strategies [12]. Piper cubeba (cubeba) or the tailed pepper is a member of genus Piper mostly known as, tailed pepper (because of the stalks attached), Java pepper (in Java) and kemukus (in Indonesia), [13]. Cubeba is a perpetual plant, with climbing stem, round branches, ash colored and its leaves are from 4 to 6, so soft flowers have a spike shape at the end of the branches with ovate-oblong, acuminate. Cubeba is one of the popular medicinal plants [14]. It is used to treat genitourinary disease Kidney and Bladder calculi [15]. Gonorrhoea, dysentery, syphilis, abdominal pain and asthma [16]. also it use as gastroprotective [17]. The effect of Piper cubeba extract on Bacteriocin of uropathogenic isolates have not been compared before so in this study, we have been detection the effect of P. cubeba extracts on Bacteriocin of uropathogenic *Escherichia coli*.

## II. MATERIAL AND METHODS

### 2.1 Collection and drying of Piper cubeba

Piper cubeba fruits were collected from the local markets Of Babylon Province then it was washed three times by D.W.P. cubeba fruits were dried by using oven at 55°C for 5 hours. The powdered samples were stored in a clean container until the time of the extraction.

### 2.2 Extract preparation

Hot water was used to prepare the extract of P. cubeba fruits. An amount of 30g. of fruit so in 100ml of hot water (100 cae%) and adjust to magnetic stirrer for 5h. Then filtered through a sterilized whatman No.1 filter paper [18, 19, 20] Filtered extracts were air dried at 40°C for 48 h. then stored in labeled sterile container in a deep freeze at -18°C until further use [21].

Phytochemical analysis of P.cubeba: Hot aqueous extract were tested chemically to identify its chemical compounds according to [22]

### 2.3 Bacterial strain

In the present study 35 *E.coli* isolates were collected from patient suffering from long term urinary tract catheters and urinary tract infection for both genera with age ranging between (11-60) years in Babylon Province, Iraq during a period from September 2015 to February 2016. Isolates were identified according to morphology, microscopic examination and biochemical tests. Bacterial cultures were maintained on nutrient broth as a basal medium, supplemented with 15% glycerol and kept at 4°C until used [23].

*Escherichia coli* was grown with (25 mg / ml) MIC concentration of P. cubeba hot aqueous extract at 37 c for 24h in tests of detection Bacteriocin production (Antibacterial activity and MIC concentration of hot aqueous extract of P.cubeba fruits was published in other research).

## 2.4 Production and extraction of crude Bacteriocin

To determine bacteriocin production, E.coli grown in 400ml m63 both at 37°C for 24 h in triplicates. The cultures were centrifuged at 4,400 rpm for 15 min at 4°C and filtrated through 0.22µm Millipore filter [24], The crude bacteriocin were then assayed using well diffusion method.

## 2.5 Precipitation of Bacteriocin

Bacteriocin precipitates from crud extraction by ammonium sulphat with saturated ratio 80%. This method was done according to method of [25] as the followed:

1. Ammonium sulphat 51.6g was gradually added to 100ml of crud extraction (CE) of bacteriocin protein with continuous mixing by magnetic stirrer at 150m for 10 min at 4c.
2. After that the solution was centrifuged at 10000rpm for 15min, the supernatant was removed and the sediment was used.
3. Phosphate buffer saline 5ml was added to the sediment (bacteriocin).

## 2.6 Measurement of Bacteriocin protein concentration

Bradford method [26] was used to measure bacteriocin protein concentration.

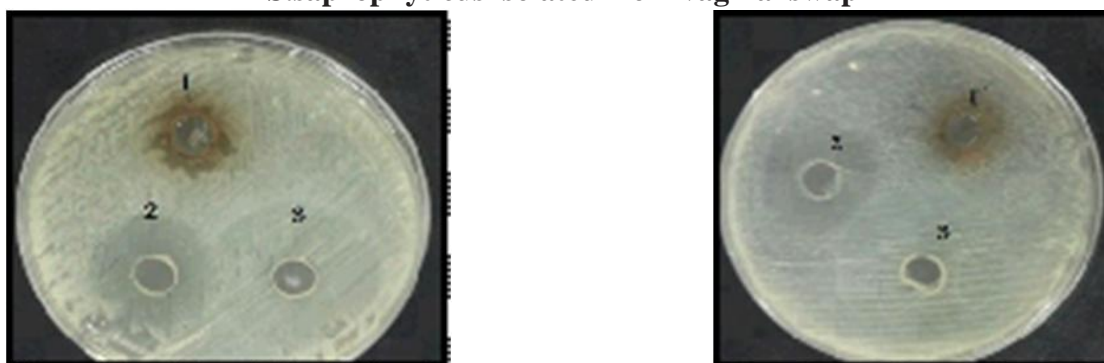
## 2.7 Antimicrobial Assay of Bacteriocin

The antibacterial action of bacteriocin isolated from E coli determined by using the well diffusion method. Amount of 50 µL of the supernatant were placed in wells with 4mm diameter on Mueller-Hinton agar plates that cultured previously with the indicator bacteria. Diameters of the zones of growth inhibition were measured after 12-18 h of incubation [27].

## 2.8 Electrophoretic separation of bacteriocin

Bacteriocin extracts were electrophoresed on SDS-PAGE according to [28].

**FIGURE 1: Antimicrobial activity of 1.Pcubeba extract 2.bacteriocin of E.coli grown with the extract 3.bacteriocin only (A) Indicator bacteria was S. saprophyticus isolated from urine (B) S.saprophyticus isolated from vaginal swap**



## III. RESULT

In the present study 35 E. coli isolates were collected from patient suffering from long term urinary tract catheters and urinary tract infection whose did not take any drug and for both genera with age ranging between (11-60) years during a period from September 2015 to February 2016 All samples were cultured on nutrient MacConkey and Blood agar plates then it was incubated at 37 for 18- 24 hours.

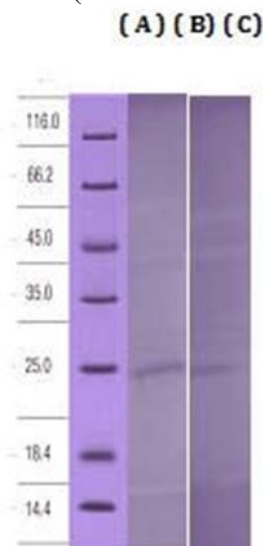
Identification of pure isolate was done by observing morphological, cultural and biochemical characters according to [29], phytochemical screening of hot aqueous *P. cubeba* extract showed it was containing glycosides, phenols, Flavonoids and tannin.

*E. coli* isolates incubated with the MIC concentration (25mg /ml) of hot aqueous extract at 37 for 24h to detect effect of hot aqueous extract of *P. cubeba* on Bacteriocin production.

### 3.1 Bacteriocin production

Bacteriocins are peptides that ribosomally synthesized have antimicrobial activity broadly distributed in nature. This peptide biodiversity is supported via many differences in their structures. All synthesized peptides, regardless of sub- classification, share a net positive charge that causes them to fold into an amphiphilic conformation on interaction with bacterial membranes [30].

**FIGURE 2: SDS-PAGE analysis of colicin protein of *E.coli* by using 12 % acryl amid gel and Commassi brilliant blue staining. (A): Ladder protein, (B): Specimen (without the extract), (C): Specimen (with the extract)**



Productions of Bacterocins are a main characteristic of *E. coli* and several species Enterobacteriaceae of family [31]. In the present study detection of bacteriocin production by *E. coli* isolates studies and was found out of 35 *E. coli* isolates only 5 (14.2%) isolates produced bacteriocin and then antimicrobial of this bacteriocin was tested [32]. Found a relationship among bacteriocin and virulence factors, in a number of virulence factors adhesins ability, cytotoxins, siderophores, etc.) was identified, that occur more frequently. In Many studies were done to detect bacteriocin production, one of these, study of [33] was found among 30 *E. coli* isolates 17(56.7%)were produced bacteriocin, while 13(43.3%) were found no ability to produce bacteriocin. [34] have been found 102 (38%) of isolates was bacteriocin producing among 266 human *E. coli* strains. similar result by [35] reported that 195 (54%) bacteriocin producing of UTI *E. coli* strains, were identified among 361 tested. An even lower frequency (32.3%) it was show that among 440 *E. coli* UTI strains [36]. and this result were similar to our findings in present study. Bacteriocin was proposed as a replacement for antibiotics to which pathogenic bacteria was become resistant. Potentially, the bacteriocin could be produced by bacteria intentionally introduced into the patient to combat infection.

In current study, (5) isolates of *E. coli* were produced bacteriocin and then bacteria grown with *P. cubeba*

extract the result showed no changes in bacteriocin production between before and after treated bacteria with *P. cubeba* extract.

Bacteriocin was precipitated by using ammonium sulphat (80%) method. The ammonium sulphat used because of its being safe, don't interfere with products and easily to dissolve, so, this salt is useful in salting out. It is separating proteins method based upon that the proteins are less soluble at high concentrations of salt. This process is as well used to concentrate dilute proteins solutions. Dialysis can be used to remove the salt if needed [37] and then bacteriocin protein concentration was measured by Bradford method [26], because it is simple and very fast method used to measure the same amount of protein that was measured by Lowey assay, commonly used to determine the total protein concentration of sample, especially for protein of cell fraction and for gel electrophoresis. It was used for measure bacteriocin concentration for both bacteria grown with and without *P. cubeba* extract and then was compared between it. In the case of bacteria cultured without extract protein concentration of partially purified (by ammonium sulphat) was (9.21mg/ml) while bacteriocin protein concentration of bacteria grown with the extract was (10.6mg/ml). The statistical analysis of result did not show significant differences and "p" value was 0.177. Purified of bacteriocin decreased portion concentration but enhance it is activity fractionation by Ammonium sulphat may increase the amount of bacteriocin activity against tested bacteria.

Assessment of antimicrobial activity of bacteriocin, *P. cubeba* extract, and bacteriocin of bacteria grown with *P. cubeba* extract via agar well diffusion method at 37 for 24h against *S. saprophyticus* isolated from vaginal swap and urine sample as indicator bacteria. As show previously the extract haven't any antimicrobial activity against *S. saprophyticus* from urine sample but it was exhibited antimicrobial effect against *S. saprophyticus* from vaginal swap with inhibition zone (10mm). In case of bacteriocin only it was show ability to inhibition growth of *S. saprophyticus* with inhibition zone (40mm) but indicator bacteria return to grow again and resist bacteriocin as shown in figure (1), whereas the Bacteriocin derived from *E. coli* grown with *P. cubeba* extract inhibited *S. saprophyticus* growth with inhibition zone (30mm) and bacteria didn't returned to grow again. *P. cubeba* extract may be effect on bacteriocin production when bacteria grown with the extract so give good inhibition to indicator bacteria, As illustrated previously activity of bacteriocin produced by bacteria were grown with the extract give inhibition zone less than bacteriocin of bacteria grown without the extract but the extract increased the activity of killing or inhibition so that indicator bacteria didn't returned to grow again [38] reported that ethanolic extracts of neem (*Azadirachta indica*) leaf produced antibacterial action on Gram positive and negative bacteria and they observed a positive synergism in terms of antibacterial potential of the extract upon combination with bacteriocin from lactic acid bacterium.

As showed in the present study bacteriocin inhibit bacterial growth that may be due to variety of mechanisms like inhibition synthesis of macromolecular, stopping protein synthesis, breakdown of DNA, or killing its targets via membrane permeabilization or degradation of nucleic acid [39; 40; 41; 6].

According to result of this study that antimicrobial activity of bacteriocin in presence of *P. cubeba* was more than that in absence the extract and bacteriocin protein concentration in presence the extract were higher than the bacteriocin concentration of *E. coli* without the extract.



### 3.2 Determination the molecular size of bacteriocin by using SDS-PAGE method

In order to determine the molecular size of the bacteriocin isolated from *E. coli* isolate (grown with and without *P. cubeba*), the bacteriocin was subjected to SDS-PAGE analysis the estimated molecular mass of bacteriocin as described by [28], Bacteriocin (for *E. coli* grown with and without *P. cubeba* extract) was found to be (25 KDa) as evidenced in SDS-PAGE. This molecular weight within the range of colicin molecular weight 25KDa- 80KDa [40]. Colicins are proteins with high molecular weight that kill the target cells via a several mechanisms. A colicin is including three domains functionally distinct; receptor recognition, protein translocation, and killing [42]. Possession of *E. coli* isolate for bacteriocin considered an indication that bacteria may be used for producing and developing of antibiotics.

The activity spectrum of colicin against other bacterial species may help in the possibility of using colicin for used as epidemiological marker by studding typing of *E. coli* or other bacterial species according to their sensitivity to the colicin [43].The molecular Wight of colicin show in figure 2.

## IV. CONCLUSION

Hot aqueous extract of *Piper cubeba* have activity on antimicrobial activity of bacteriocin of *E. coli*. *Piper cubeba* may serve as auxiliary agents that can enhance standard conventional antibacterial therapy in UTIs. Activity of *Piper cubeba* on bacteria is still not completely known and needed more studies.

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# Formulation and Evaluation of Acyclovir by Quality and Design based on Microsponges

Kranti Kumar Bajpai<sup>1\*</sup>, Sangamesh B. Puranik<sup>2</sup>, Rohit Saraswat<sup>3</sup>, Prashant Sharma<sup>4</sup>,  
Ritu Sharma<sup>5</sup>

School of Pharmacy, OPJS University, Churu, Rajasthan, India

## Abstract—

**Objective:** The proposed study is focussed at developing acyclovir microsponges for oral drug delivery systems. QbD was applied for better understanding of the process and to generate design space, using quality target product profile, critical quality attributes, and risk assessment. The aim of the experiment is to prepare a safe, efficacious, stable and patient compliant microsphere dosage form of Acyclovir.

**Materials and methods:** Pre-formulation studies were carried out which helped in developing a suitable dosage form. UV, FTIR, DSC, and SEM studies were done for pre-formulation and post-formulation evaluations. QbD was applied to generate design space, using QTPP, CQA, and risk assessment. Microsponges of acyclovir were developed by 2<sup>3</sup> factorial designs. Three variables Drug: Polymer ratio (X1), Concentration of surfactant (X2) and Stirring speed (RPM) (X3) at two levels low and high were selected and response surface plots were generated. The microsponges were prepared by Quasi-emulsion solvent diffusion method. Various characterizations that were carried out include entrapment efficiency, percentage yield, particle size determination, in-vitro drug release studies and kinetic modelling of drug release. Statistical analyses of batches and surface response studies were done to understand the effect of various independent variables on the dependent variables.

**Results and Discussions:** The  $\lambda_{max}$  was confirmed at 251 nm by UV spectroscopy. The melting point was determined experimentally to be 246°C which confirms the drug to be Acyclovir. FTIR and DSC studies confirmed that the drug is Acyclovir. Eight trials were taken as per the by 2<sup>3</sup> factorial designs.

**Conclusion:** The study indicates that microsponges of Acyclovir by QbD approach were successfully developed.

**Keywords—** Microsphere, Acyclovir, DoE, QbD.

## I. INTRODUCTION

Acyclovir is a potent, specific antiviral drug which is active against herpes simplex viruses' types I and II and varicella zoster virus [1]. Literature studies indicate that the oral bioavailability of acyclovir is relatively less, which is around 20-30%. Hence there is a need for enhancement of oral bioavailability of the acyclovir drug by employing various approaches. Acyclovir is available as various dosage forms in the market which includes capsules, creams, ointments, tablets and suspension. For all oral dosage forms the limiting factor of bioavailability which is poor. In order to overcome this limitation of oral delivery of Acyclovir, attempts have to be made to develop novel drug delivery systems of the same drug. The underlying aim of the proposed investigation is to augment the oral bioavailability of acyclovir by developing a microsphere drug delivery system of acyclovir which will attempt to increase the oral bioavailability of the drug. Microsponges are spherical small structures having large void spaces where there can be entrapment of the drug.



These voids are non-collapsible; hence it is better for drug entrapment and the entrapment efficiency of microsponges would be very high. The release of the drugs from the microsponges involves the movement of the drug from these non-collapsible void spaces to outside. The presence of such void spaces may enable the microsponges to deliver the drug slowly over a period for prolonged time<sup>2</sup>. As such drug delivery systems are devoid of much irritation and are capable of prolonged activity; they can enhance the patient compliance. Quality by design (QbD) is an intelligent way to bring quality into both product and process. QbD can be achieved by constructive planning of all the previous data that is accessible. Although it is based on certain amount of risks, it provides results that minimizes the risk of end product failure and enhances the chances of regulatory acceptance<sup>3</sup>. ICH Q8, ICH Q9 and ICH Q10 do explain the principles of QbD in the best way. They provide guidelines on science and risk based assessment, life cycle of product and various approaches in its development. It is also well known fact that there can be a great deal of unpredictability in scale up of a product from research and development, although the reason for failure is not generally understood. QbD is an approach to be applied in all stages of drug discovery, production and delivery [4-6].

## II. MATERIALS AND METHODS

### 2.1 Materials

The drug Acyclovir was obtained as gift sample from Aurobindo Pharma, Hyderabad. All other chemicals that were used in the experiment were of the analytical grade.

### 2.2 Methods

#### 2.2.1 Pre-formulation studies

- Determination of melting point of Acyclovir:

Melting point of Acyclovir was determined by open capillary method.

Determination of wavelength maxima ( $\lambda_{max}$ ) of Acyclovir: Determination of wavelength maxima ( $\lambda_{max}$ ) was done for Acyclovir.

- Preparation of calibration curve for Acyclovir:

The calibration curve of Acyclovir was plotted by taking 0.1N HCl as the solvent.

- Identification of Acyclovir by FT-IR Spectroscopy:

FTIR study was carried for Acyclovir.

Identification of Acyclovir by DSC Study:

The thermograph of Acyclovir was obtained by DSC.

#### 2.2.2 Method of preparation of Acyclovir microsponges:

Microsponges are prepared by quasi-emulsion solvent diffusion technique. In this method external phase and internal phases are used. The internal phase is organic phase was containing drug (acyclovir), Dichloromethane, Eudragit RS100 and triethyl citrate (TEC) which is added in order to facilitate the plasticity. The external phase consisted of distilled water and polyvinyl alcohol (PVA) which acts as surfactant. Measured amounts of drug and polymer are dissolved in measured quantity of DCM. The formed solution is poured into water containing polyvinyl alcohol. Internal phase and external phases

were properly mixed. This results in the solidification of the drug and its diffusion out of the liquid phases. Finally the solidified microsponges are collected by filtration. Then they are subjected to washing and drying.

## 2.3 Characterization of Acyclovir microsponges:

### 2.3.1 Drug content:

Drug content is determined by using the UV Visible spectrophotometer.

### 2.3.2 Average particle size analysis:

Malvern apparatus was used for particle size analysis

### 2.3.3 In-vitro drug release study of microsponges:

Dissolution test was carried out to determine the in-vitro drug release profile of the prepared batches of microsponges.

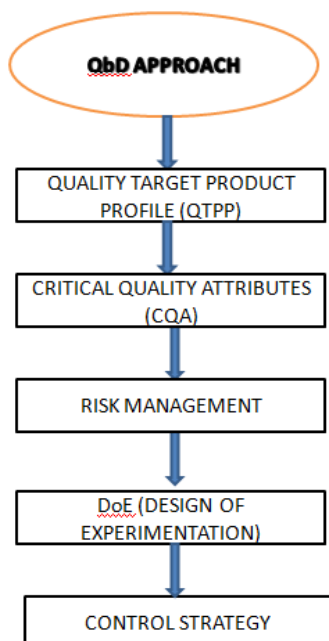
### 2.3.4 Kinetics of drug release:

Kinetic release study was performed to find drug release mechanism from dissolution parameter by using different various kinetic model equations like Zero order, First order, Higuchi, Hixon-Crowell and Korsemeyer-Peppas model.

### 2.3.5 Risk Assessment to identify CQAs affecting drug product quality:

Risk assessments was done to select formulation and process variable which may affect product quality for CQAs by process characterization that defines satisfactory changes in material and process parameters. As a final point, this can result in quality assurance by process design space to understand and develop control strategy. Critical quality attributes were categorized into high, medium and low risk parameters based on knowledge space. Usually high-risk parameters are considered important for Design of Experiments as they are having more effect than others and need to be in accepting multivariate ranges.

FIGURE 1: QbD approach



**TABLE 1**  
**INDEPENDENT AND DEPENDENT VARIABLES**

Independent variables – X	Dependent Variables – Y
<b>Polymer Type and Concentration</b>	Particle Size
<b>Drug: Polymer Ratio</b>	
<b>Internal Phase Type</b>	Entrapment Efficiency (%)
<b>Internal Phase Volume</b>	
<b>External Phase Volume</b>	Drug content
<b>Surfactant Type and Its Concentration</b>	
<b>Stirring Speed and Time</b>	% Cumulative Drug Release

Effect of different independent variables were checked by evaluating particle size, entrapment efficiency (%), particle size and % cumulative drug release of Acyclovir microsponges formulated in preliminary trial batches. Based on that characterization, CQAs were selected which have greater effect on microsponges formulations.

### 2.3.6 Design of Experimentation (DoE) of Acyclovir microsponges by using QbD approach:

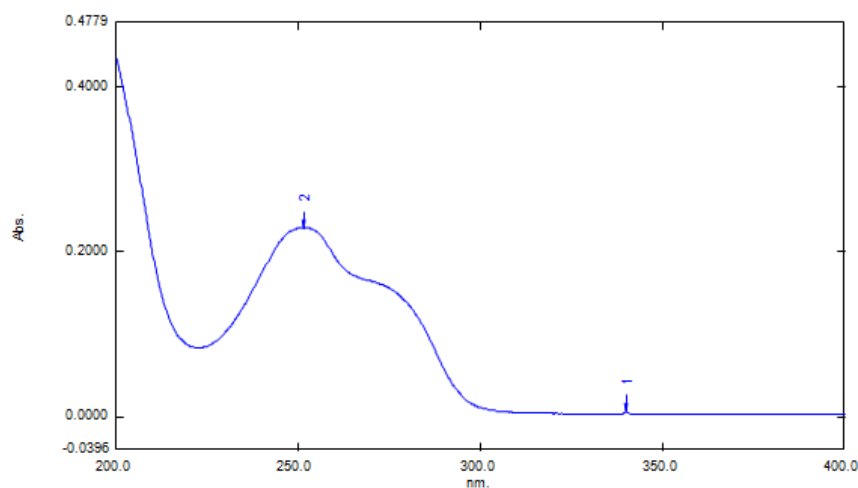
A design space can signify formulation and process variables that affects attributes which are related to drug substance, materials, equipments and finished product quality. For this purpose, risk assessment was done based on understanding of process and formulation related parameters on microsponges' quality. Preliminary studies and later Design of Experimentation (DoE) was carried out for high risk parameters. Based on effect of critical quality attributes of target product profile, design space for obtaining robust formulation was proposed.

## III. RESULTS AND DISCUSSIONS

### 3.1 Pre-formulation studies

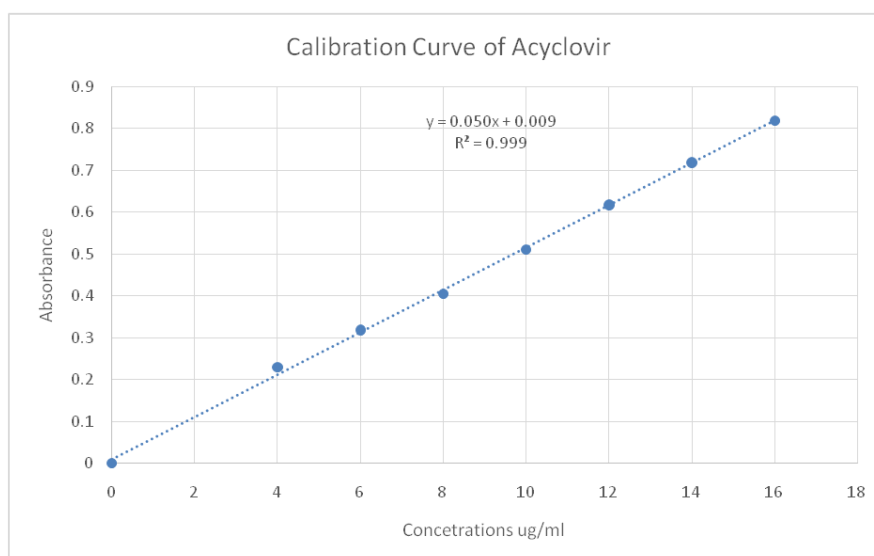
#### 3.1.1 Determination of melting point of Acyclovir:

- The melting point of Acyclovir was found to be 256.5 °C.
- Determination of wavelength maxima ( $\lambda_{max}$ ) of Acyclovir:
- The wavelength maxima ( $\lambda_{max}$ ) of Acyclovir were found to be 251 nm.



**FIGURE 2: Wavelength max ( $\lambda_{max}$ ) of Acyclovir**

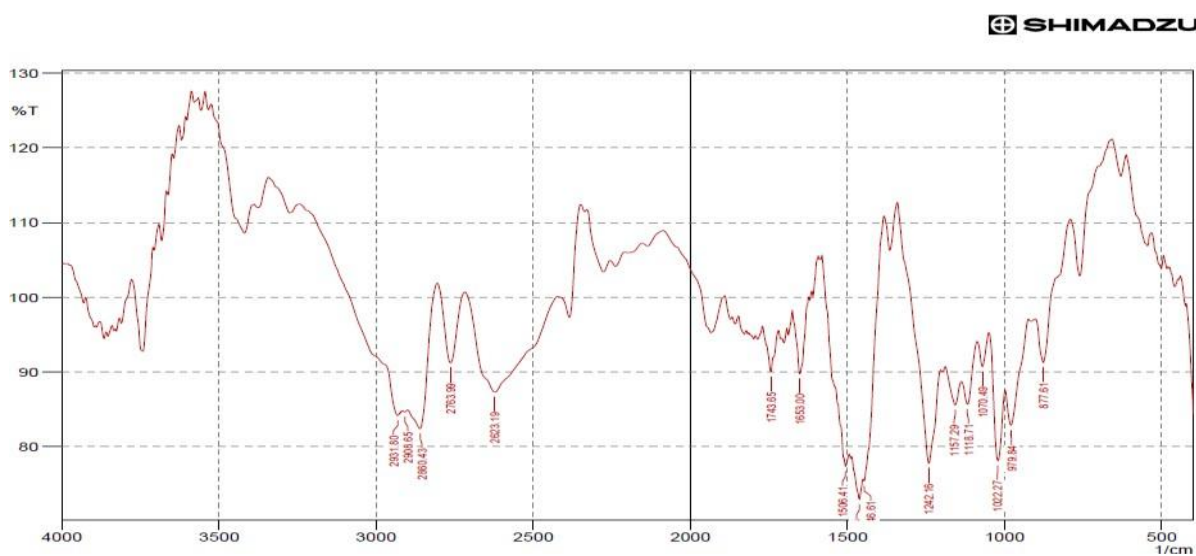
### 3.2 Preparation of calibration curve for Acyclovir:



**FIGURE 3 Calibration curve for Acyclovir**

### 3.3 Identification of Acyclovir by FT-IR Spectroscopy:

The recorded IR spectrum of Acyclovir is shown in following figure.



**FIGURE 4: FTIR spectrum of Acyclovir**

**TABLE 2**  
**FT-IR PEAKS OF ACYCLOVIR**

Type of Vibration	Standard Wave number( $cm^{-1}$ )	Observed Wave number( $cm^{-1}$ )
C=C Stretching of Aromatic	1600-1475	1465.90
- tretching of amine	3500-3300	3417.88
N-O Stretching of N - Oxide	1300-1200	1222.87
C-H Stretching of Piperidines	2850-3000	2937.59
C-N Stretching of C-NH <sub>2</sub>	860-766	761.88

### 3.4 Identification of Acyclovir by DSC Study

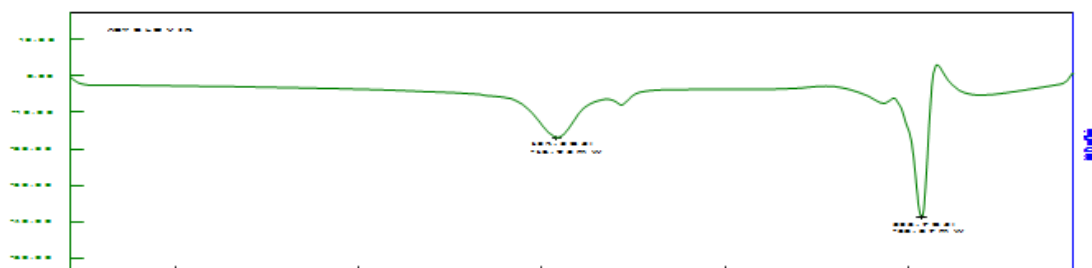


FIGURE 5: DSC thermograph

### 3.5 $2^3$ Factorial Design for Acyclovir microsponges

Various batches of Acyclovir microsponges by DoE Using QbD approach were prepared according to 23 factorial designs which are as shown in Table 3.

TABLE 3  
 $2^3$  FACTORIAL DESIGN

Independent Variables	Low (-)	High (+)
Drug: Polymer ratio (X1)	1:1	2:1
Concentration of surfactant (X2)	0.75%	1%
Stirring speed (RPM) (X3)	1500	2000
Dependent Variables		
Y1 = % Yield		
Y2 = % Entrapment efficiency		
Y3 = Particle Size		
Y4 = % CDR		

### 3.6 Compositions of Factorial Batches in Coded Form

Various batches of Acyclovir microsponges with Eudragit RS 100 were prepared according to 23 factorial designs which are as shown in Table 4.

TABLE 4  
COMPOSITIONS OF FACTORIAL BATCHES IN CODED FORM

Batch No.	$2^3 = 8$ Batches		
	Variable level in coded form		
	Drug: Polymer Ratio (X1)	Concentration of surfactant (X2)	Stirring speed (RPM) (X3)
1	-1	-1	-1
2	+1	-1	-1
3	-1	+1	-1
4	+1	+1	-1
5	-1	-1	+1
6	+1	-1	+1
7	-1	+1	+1
8	+1	+1	+1

### 3.7 Formulation Design by 2<sup>3</sup> Factorial Design

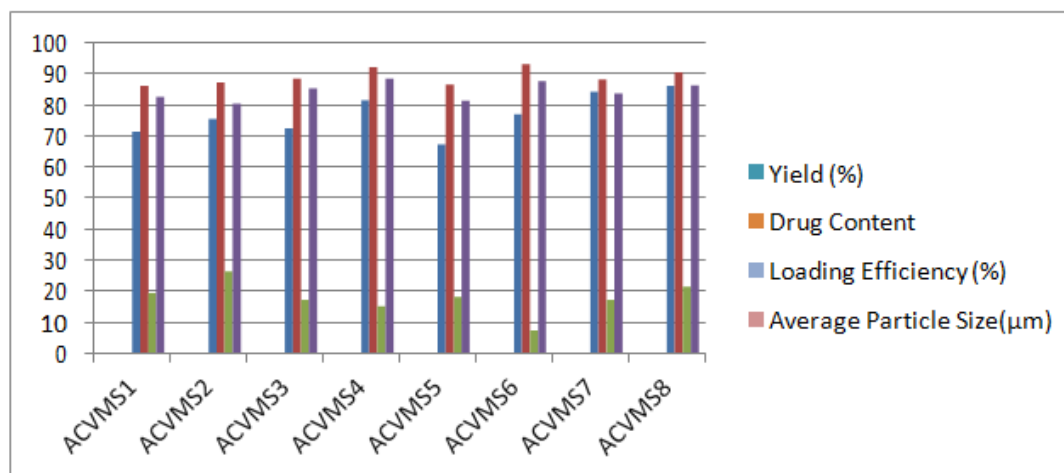
**TABLE 5**  
**FORMULATION DESIGN BY 2<sup>3</sup> FACTORIAL DESIGNS**

Batch	Drug: Polymer Ratio (X1)	Concentration of surfactant (X2)	Stirring speed (RPM) (X3)
ACVMS1	1:1	0.75	1500
ACVMS2	2:1	0.75	1500
ACVMS3	1:1	1	1500
ACVMS4	2:1	1	1500
ACVMS5	1:1	0.75	2000
ACVMS6	2:1	0.75	2000
ACVMS7	1:1	1	2000
ACVMS8	2:1	1	2000

### 3.8 Characterization of Acyclovir microsponges:

**TABLE 6**  
**CHARACTERIZATION OF BATCHES ACVMS1- ACVMS8**

Batch No	Yield-% (Y1) (Mean ± S.D.) (n = 3)	E.E.-% (Y2) (Mean ± S.D.) (n = 3)	P. Size-µm (Y3) (Mean ± S.D.) (n = 3)	Drug Content (Mean ± S.D.) (n = 3)
ACVMS1	71.45±1.15	86.25±1.82	19.42±2.54	82.66±1.55
ACVMS2	75.52±1.66	87.28±1.97	26.46±2.76	80.46±1.20
ACVMS3	72.48±1.85	88.56±1.54	17.25±1.18	85.38±2.33
ACVMS4	81.49±2.24	92.28±1.77	15.23±1.87	88.57±1.44
ACVMS5	67.38±1.52	86.66±1.65	18.29±1.60	81.39±1.56
ACVMS6	77.13±1.38	93.14±1.44	7.4±1.74	87.63±1.75
ACVMS7	84.18±2.28	88.19±1.89	17.22±1.67	83.82±2.65
ACVMS8	86.17±1.49	90.52±2.73	21.51±2.23	86.32±1.78



**FIGURE 6: Characterization of Batches ACVMS1 – ACVMS8**

### 3.9 % Cumulative Drug Release profile of batches ACVMS1- ACVMS8

TABLE 7

% CUMULATIVE DRUG RELEASE PROFILE OF BATCHES ACVMS1 – ACVMS4

Time	ACVMS1 (Mean ± SD) (n=3)	ACVMS2 (Mean ± SD) (n=3)	ACVMS3 (Mean ± SD) (n=3)	ACVMS4 (Mean ± SD) (n=3)
0	0	0	0	0
1	28.01±1.13	14.18±1.78	15.16±1.45	21.25±1.49
2	37.81±1.74	18.21±1.46	17.30±1.17	27.81±1.65
3	44.95±1.56	26.84±1.29	22.85±1.59	36.38±1.37
4	56.25±1.93	32.59±1.66	31.37±1.17	46.90±1.58
5	63.45±1.63	43.20±1.52	42.61±1.79	51.48±1.48
6	76.11±1.28	54.01±1.68	53.33±1.62	66.37±1.75
7	85.26±1.82	65.01±1.84	66.08±1.28	81.42±1.81
8	90.32±1.25	78.06±1.94	75.91±1.56	88.96±1.26

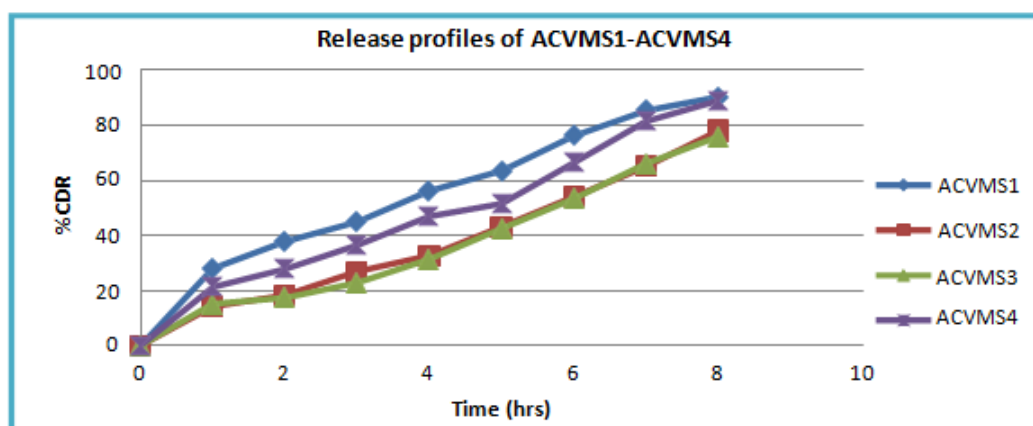


FIGURE 7: % Cumulative Drug Release profile of Batches ACVMS1 – ACVMS4

TABLE 8

% CUMULATIVE DRUG RELEASE PROFILE OF BATCHES ACVMS5 – ACVMS8

Time	ACVMS5 (Mean ± SD) (n=3)	ACVMS6 (Mean ± SD) (n=3)	ACVMS7 (Mean ± SD) (n=3)	ACVMS8 (Mean ± SD) (n=3)
0	0	0	0	0
1	16.33±1.17	28.01±1.87	21.73±1.54	17.88±1.93
2	21.44±1.67	37.84±1.64	30.35±1.71	26.45±1.56
3	31.76±1.65	44.95±1.92	46.31±1.95	36.97±1.76
4	40.67±1.39	56.25±1.66	56.34±1.62	38.72±1.82
5	51.18±1.36	63.45±1.25	61.80±1.48	60.95±1.19
6	61.48±1.82	76.11±1.86	71.82±1.26	73.38±1.17
7	74.94±1.28	85.26±1.48	84.87±1.82	84.87±1.42
8	85.55±1.52	90.32±1.49	93.24±1.65	91.74±1.62

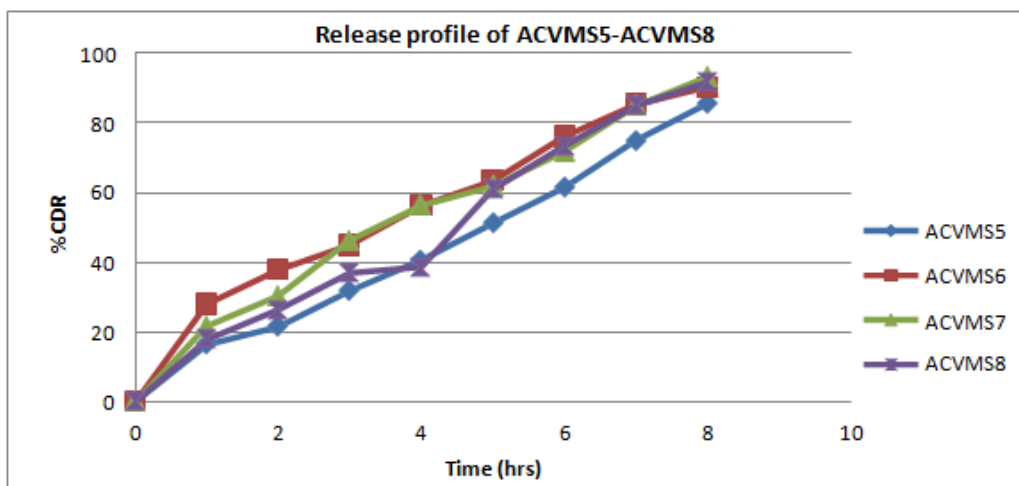


FIGURE 8: Cumulative Drug Release profile of Batches ACVMS5 – ACVMS8

TABLE 9  
RELEASE KINETIC OF BATCHES ACVMS1 – ACVMS4

Model	Parameter	ACVMS1	ACVMS2	ACVMS3	ACVMS4
Zero Order	R <sup>2</sup>	0.9468	0.9829	0.9609	0.9733
	Slope	10.299	8.4804	8.2129	10.202
	Intercept	11.45	2.4204	2.0214	5.7064
First Order	R <sup>2</sup>	0.9688	0.9654	0.9338	0.9673
	Slope	-0.0956	-0.0532	-0.0513	-0.073
	Intercept	1.9886	2.0048	2.0067	1.9988
Higuchi Model	R <sup>2</sup>	0.9856	0.9899	0.9859	0.9865
	Slope	30.03	21.123	20.267	25.136
	Intercept	- 1.8141	- 4.825	- 4.7016	- 6.3716
Hixon Crowell	R <sup>2</sup>	0.9757	0.9752	0.9462	0.9775
	Slope	0.2699	0.1669	0.1611	0.2183
	Intercept	0.0997	0.0055	- 0.0014	0.042
Korsmeyerpeppas equation	R <sup>2</sup>	0.8786	0.8938	0.8432	0.9089
	Slope	74.833	54.858	52.188	66.878
	Intercept	14.108	5.4689	5.3575	9.0138

TABLE 10  
RELEASE KINETIC OF BATCHES ACVMS5 – ACVMS8

Model	Parameter	ACVMS5	ACVMS6	ACVMS7	ACVMS8
Zero Order	R <sup>2</sup>	0.9867	0.9467	0.97	0.9679
	Slope	10.049	11.451	11.735	11.413
	Intercept	2.1189	10.306	6.5582	2.8125
First Order	R <sup>2</sup>	0.964	0.9688	0.9935	0.9103
	Slope	-0.0687	-0.0956	-0.0915	-0.0889
	Intercept	2.0155	1.9886	2.0019	2.03
Higuchi Model	R <sup>2</sup>	0.9968	0.9856	0.9938	0.9827
	Slope	24.896	30.029	30.221	28.326
	Intercept	- 6.2585	- 1.8083	- 5.0004	- 6.7818
Hixon Crowell	R <sup>2</sup>	0.9767	0.9757	0.9934	0.9386
	Slope	0.2089	0.2699	0.2651	0.2573
	Intercept	- 0.0177	0.0999	0.0439	- 0.0387
Korsmeyerpeppas equation	R <sup>2</sup>	0.899	0.8785	0.9429	0.8798
	Slope	65.068	74.827	78.487	73.807
	Intercept	5.7057	14.115	9.7267	6.9227



### 3.10 Statistical analysis of batches ACVMS1- ACVMS8

In factorial design, amount of drug (ACV): polymer (Eudragit RS100) ratio (X1), amount of PVA Concentration (X2), and Stirring Speed (X3) were taken as independent variables. % Yield (Y1), % E. E (Y2). Particle sizes (Y3), % CDR (Y4) were selected as dependent variables.

#### 3.11 Effect on % Yield (Y1) - Surface Response Study

$$Y1 (\% \text{Yield}) = 77.73 + 5.52 * X1 + 1.44 * X2 - 2.86 * X3$$

Positive value for coefficient of X1 in equation indicates Increase in yield with Drug Concentration. Positive value of coefficient of X2 PVA concentration indicates increase in response of Y1 i.e. % yield. Negative value of coefficient X3, time indicates decrease in yield.

#### 3.12 Effect on % Entrapment Efficiency (Y2) - Surface Response Study

##### 3.12.1 Entrapment Efficiency (Y2) =

$$84.75 + 0.875 * X1 + 0.55 * X2 + 1.05 * X3$$

Positive value for coefficient of X1 in equation indicates increase in Entrapment Efficiency with Drug Concentration. Positive value of coefficient of X2 PVA concentration indicates increase in response of Y2 i.e. % E.E. Positive value of coefficient X3, time indicates increase in yield.

#### 3.13 Effect on Particle Size (Y3) - Surface Response Study P.S. (Y3) = 18.85 - 2.51 \* X1 + 2.26 \* X2 - 3.31 \* X3

Negative value for coefficient of X1 in equation indicates decrease in particle Size with Drug Concentration. Positive value of coefficient of X2 PVA concentration indicates increase in response of Y3 i.e. P.S. Negative value of coefficient X3, time indicates decrease in Particle size.

#### 3.14 Effect on % CDR (Y4) - Surface Response Study

$$\% \text{CDR (Y4)} = 87.03 + 4.54 * X1 - 2.86 * X2 - 0.84 * X3$$

Positive value for coefficient of X1 in equation indicates Increase in CDR with Drug Concentration. Negative value of coefficient of X2 PVA concentration indicates decrease in response of Y4 i.e. % CDR. Negative value of coefficient X3, time indicates decrease in CDR.

## IV. CONCLUSION

The focus of the current study was to develop microsphere drug delivery system of acyclovir using QbD approach. Literature studies indicate that the oral bioavailability of acyclovir is relatively less, which is around 20-30%. The underlying objective of the proposed investigation is to augment the oral bioavailability of acyclovir by developing a microsphere drug delivery system of acyclovir. Pre-formulation studies were carried out which helped in developing a suitable dosage form. UV, FTIR, DSC, and SEM studies were done for pre-formulation and post-formulation evaluations. QbD was applied to generate design space, using QTPP, CQA, and risk assessment. Microspheres of acyclovir were developed by 2<sup>3</sup> factorial designs. Three variables Drug: Polymer ratio (X1), Concentration of surfactant (X2) and Stirring speed (RPM) (X3) at two levels low and high were selected and response surface plots were generated. The microspheres were prepared by Quasi-emulsion solvent diffusion method. Various characterizations that were carried out include entrapment efficiency, percentage yield, particle size determination, in-vitro drug release studies and kinetic modeling of drug release. Statistical

analyses of batches and surface response studies were done to understand the effect of various independent variables on the dependent variables. Lastly it was concluded that microsponges of Acyclovir using QbD approach were successfully developed.

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