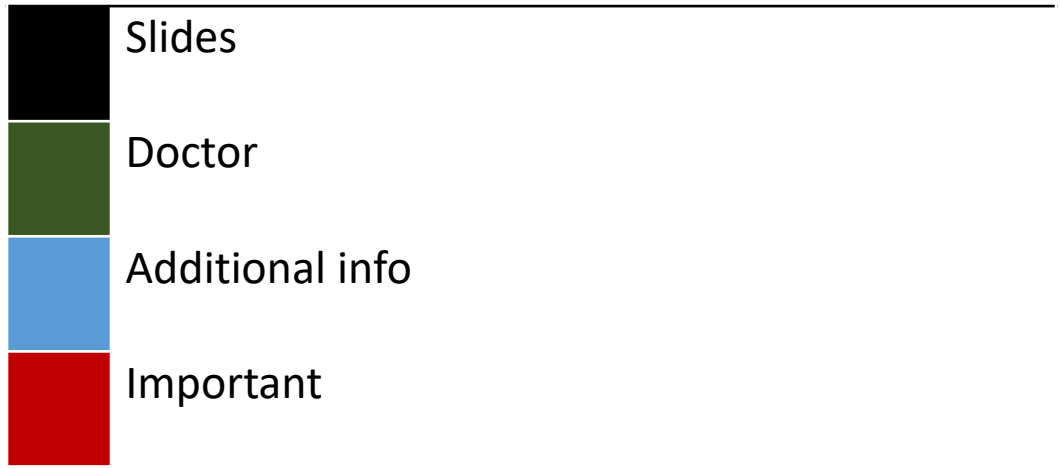

MEDICAL RESEARCH
MODIFIED NO. 9
كتابة: لجين بلال و ميس سلمان
تدقيق: محمد مجيد
الدكتور: د. منير أبو هلالة

Color code



Overview of study designs I
Observational descriptive studies
Part 1:

Dr Munir Abu-Helalah

MD,MPH,PHD

Associate Professor of Epidemiology and Preventive Medicine

Department of Family and Community Medicine

School of Medicine

Director, Public Health Institute, Jordan University

Part 1

- Descriptive studies

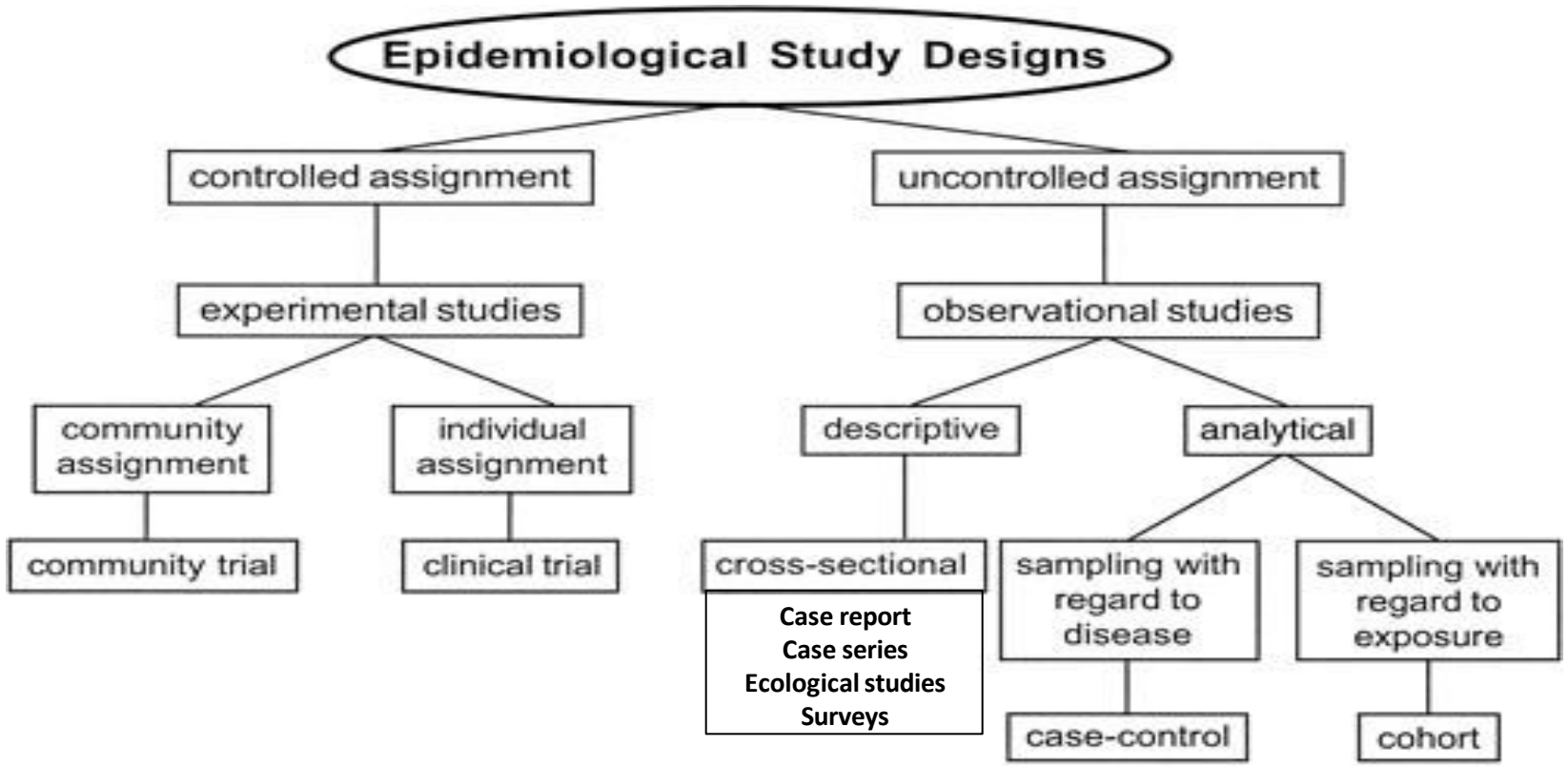
Study design: Definition

A study design is a specific plan or protocol for conducting the study, which allows the investigator to translate the conceptual hypothesis into an operational one.

this is the pathway that we're going to follow your study :

I want to do study on the prevalence of diabetes → cross-sectional study
to study new intervention for type two diabetes → clinical trial.
I need to look at risk factors of type two diabetes → cohort study

So this is the pathway or the plan that you're going to follow to reach your outcomes or to answer the study questions



Source: Waning B, Montagne M: *Pharmacoepidemiology: Principles and Practice*: http://www.accesspharmacy.com

We classify epidemiological studies into : Controlled and uncontrolled assignments

Again and again and again …..

1- Controlled assignment :

In controlled assignment studies, the investigator actively assigns treatments or interventions to study participants. This approach is used to understand the effects of an intervention by comparing treated and control groups.

A- Clinical trials examples:

- **Clinical Trial – Treatment Trial:** The investigator administers an intervention to treat a disease.
- **Example:** Previous research suggests aspirin may reduce colorectal cancer risk. In a controlled assignment study, participants are randomized into two groups: one receives 100 mg of aspirin, and the other receives a placebo. Both groups are then followed to observe outcomes.
- **Clinical Trial – Preventive Trial:** investigator provides an intervention to prevent disease among healthy individuals.
- **Example:** Administering aspirin to participants without colorectal cancer to evaluate its preventive potential.

Controlled assignments can also involve comparisons of medical procedures or approaches:

- **Surgical Comparison:** Comparing outcomes of laparoscopic cholecystectomy with open cholecystectomy.
- **Physiotherapy Referral Timing:** Patients with severe lower back pain are randomized into two groups: one receives physiotherapy within 48 hours, and the other follows the routine referral schedule (two weeks). Both groups undergo the same physiotherapy sessions, with pain scale, quality of life, and physical activity assessed after six weeks.
- **Referral Specialties for Newly Diagnosed Conditions:** Newly diagnosed diabetic patients are randomized to receive treatment at either a primary healthcare facility or a family medicine clinic. After one year, outcomes such as HbA1C levels are compared.

B- Community Trials examples:

In community trials, the intervention is assigned to communities rather than individuals. This approach assesses the impact of interventions on a broader scale.

- **Example 1:** To improve medical research participation, Jordan University students receive workshops and lectures on research, while JUST students receive posters, leaflets, emails, and e-learning videos. Research participation rates are compared after one year.
- **Example 2:** To reduce smoking rates among secondary school students, students in Mafraq receive leaflets and posters, while students in Irbid receive lectures and workshops. Outcomes are assessed after one year.
- **Example 3:** Increasing fluoride in Aqaba's water supply to evaluate pediatric dental caries. A control group maintains a standard fluoride level, and outcomes are compared between Aqaba and the control city after five years.

2- Uncontrolled assignment :

In uncontrolled assignment studies, the investigator observes without intervening. These studies are useful for understanding natural outcomes without influencing participant behavior.

Example 1
(Aspirin and Cancer Prevention)
To examine aspirin's role in preventing colorectal cancer without administering the drug, records from patients already taking aspirin for other conditions can be analyzed. Patients taking either 100 mg or 325 mg aspirin are identified and compared to those not on aspirin to see the difference in colorectal cancer incidence.

Example 2

(Referral Site Study)

For glycemic control in newly diagnosed type 2 diabetes patients, outcomes are compared between those seen at a family medicine clinic and those seen at general practice. No assignments or referrals are made by the investigator—only observational data is used.

Types of Observational Studies:

A. Descriptive Studies:

Descriptive studies outline characteristics or trends without exploring cause-and-effect.

1. **Surveys:** Capture data on attitudes, beliefs, quality of life, etc., within different groups or demographics.

2. **Cross-Sectional Studies:** A type of survey assessing disease prevalence at a single point in time or over a defined period.

• **Example:** in studying the burden of type 2 diabetes in Jordan, researchers could sample 10,000 individuals from diverse regions. Participants would answer whether they have type 2 diabetes, with blood samples collected to identify undiagnosed cases(In chronic illnesses like type two diabetes, subclinical hypothyroidism,hypertension even cancer we have a good number of subjects in the community who have the disease without knowing). This approach provides a more accurate estimate of true prevalence by combining known and newly diagnosed cases.

3. **Case Reports and Case Series:**

• **Case Report:** Describes a unique or rare condition in a single patient.

• **Case Series:** Describes similar findings in a group of patients.

4. **Ecological Studies:** Uses data from large organizations (e.g., WHO) to correlate population-level risk factors with disease incidence.

• **Example:** Comparing colorectal cancer rates and red meat consumption across countries. Hypotheses can be generated from observed associations, such as “Red meat may be a risk factor for colorectal cancer.”

Types of Observational Studies:

A. Analytical Studies:

Analytical studies aim to establish associations between potential risk factors and health outcomes. The two main types are *cohort* and *case-control studies*.

Cohort Studies

Cohort studies are ideal for studying the effects of a single risk factor on multiple health outcomes. Participants are grouped by exposure status (e.g., smokers vs. non-smokers) and followed over time to observe disease incidence. For example, if examining smoking's effect on type 2 diabetes, a cohort of smokers and non-smokers without diabetes is followed, and new cases are documented. Cohort studies are generally inappropriate for rare diseases due to the need for large sample sizes.

Case-Control Studies

Case-control studies are suitable for rare diseases. Here, cases with a specific disease are compared to controls without the disease to identify potential risk factors retrospectively. For example, if studying congenital heart disease risk factors, cases of infants with congenital heart disease are compared to controls born at the same hospital without the disease. Researchers can investigate variables such as maternal age, medications taken during pregnancy, or dietary factors.

Choosing Between Study Types

1. Rare Disease

use Case-Control Study:

If you want to study a **rare disease**, the appropriate study design is a **case-control study**. In this design, you start with individuals who already have the disease and compare them to individuals who do not have the disease.
• **Why Case-Control Study**: Since rare diseases have a low prevalence, it's difficult to study them through other designs, such as cohort studies. A case-control study allows you to focus on individuals with the disease (cases) and look back at their exposures or risk factors.

Example:
• You want to study **lung cancer** (a rare disease).
• You identify 200-300 patients who have lung cancer (cases).
• You compare them with a matched group of individuals who do not have lung cancer (controls).
• You then examine whether certain exposures (e.g., radiation therapy during childhood) are more common in the lung cancer group.

Why Not Use Cross-Sectional Study for Rare Disease:

• **Problem**: Cross-sectional studies are not suitable for rare diseases because you need a large sample size to observe enough cases. A rare disease will have a very low prevalence, meaning it would take a huge sample size to capture even a small number of cases.
• **Alternative**: To understand the **magnitude** or **burden** of a rare disease, you need a **cohort study**, not a cross-sectional one, to measure the incidence over time.

2. Rare Risk Factor

use Cohort Study for Rare Risk Factor:

If you need to focus on **rare risk factors**. For rare risk factors, a **cohort study** is the best approach.

• **Why Cohort Study**: You begin with individuals who have been exposed to the rare risk factor and follow them over time to see if they develop the disease. You compare the exposed group with a matched control group who has not been exposed to the rare risk factor.

Example:

• You are studying the **risk of lung cancer** in individuals who were exposed to **radiation therapy** during childhood (a rare risk factor).

• You select a group of children who received radiation therapy and follow them over time to check for the incidence of lung cancer.

• You also select a matched control group (children who did not receive radiation therapy) to compare the rates of lung cancer.

3. Rare Disease vs. Rare Risk Factor

• **Rare Disease** → Start with a **case-control study**. You begin with patients who have the rare disease and investigate their past exposures.

• **Rare Risk Factor** → Start with a **cohort study**. You begin with individuals who have been exposed to the rare risk factor and follow them to see if they develop the rare disease.

4. Incidence vs. Prevalence

• **Incidence** refers to the **rate of new cases** of a disease over time (how many new cases appear).

• For rare diseases, **incidence studies** are more important because the number of new cases is the key focus. For example, studying the **incidence of congenital heart disease** in pregnant women in Jordan involves following a large cohort (e.g., 200,000 pregnant women) for a year to determine how many develop the condition.

• **Prevalence** refers to the **total number of cases** (existing and new) in a population at a specific point in time.

• For rare diseases, the prevalence will be very low, and it may require studying a large sample (e.g., millions of individuals) to observe even a small number of cases.

TO SUM UP:

- **For Rare Disease** → Use a **Case-Control Study** (start with patients who have the rare disease).
- **For Rare Risk Factor** → Use a **Cohort Study** (start with individuals exposed to the rare risk factor).
- **To Study Magnitude and Incidence of a Rare Disease** → Use a **Cohort Study** to follow individuals over time and observe the incidence (not prevalence because it is very small).

Observational epidemiology

- Provides information about disease patterns or drug use problems by various characteristics of person, place, and time.

- It also is used by epidemiologists to generate hypotheses regarding the causes of disease or drug use problems.

Using descriptive and then we can test them through analytical studies

Observational epidemiology

a. Descriptive

Case reports and case series

Descriptive analysis (Person place time)

Ecological (correlational)

Cross-sectional

b. Analytical

Case Control

Cohort

Epidemiological studies

- Observational studies are descriptive or analytical in nature.

- Descriptive studies attempt to uncover and portray the occurrence of the condition or problem, whereas analytical studies determine the causes of the condition or problem.
- Investigators in observational studies may plan and identify variables to be measured, but human intervention is not a part of the process.
- Experimental studies, in contrast, involve intervention in ongoing processes to study any resulting change or difference. (use medication, referral)

Observational epidemiology

- Descriptive studies: provide insight, data, and information about the course or patterns of disease or drug use problems in a population or group.

- Analytical studies are used to test cause–effect relationships, and they usually rely on the generation of new data.

Descriptive study especially the Cross-sectional studies provide essential information about the prevalence of illnesses, risk factors, and complication rates within a population. Understanding these aspects is crucial for improving public health in any country. Without knowing the common healthcare issues that affect a community, it's challenging to implement effective health interventions.

For instance, to address the burden of diseases in Jordan, we need to conduct cross-sectional studies to determine the prevalence and distribution of risk factors and complications associated with conditions like ischemic heart disease, hypertension, and diabetes. By understanding how these issues affect the population, we can take steps to reduce disease complications and improve overall health outcomes.

Additionally, analytical studies play a key role in identifying specific risk factors for various illnesses, which further aids in disease prevention and control efforts.

Case Reports and Case Series

Case report is detailed report by one or more clinicians of the profile of a single patient.

Example: 1961; pulmonary embolism 5 weeks after use on oral contraceptive.

Question: Are women who develop pulmonary embolism more likely to have used oral contraceptives than women who did not develop the disease?

If you've conducted a complex surgery and want to share your experience, experienced side effects from a medication that you think others should know about, or encountered a rare syndrome that you want to describe.

Case Series describes the characteristics of a number of patients with a given disease.

Application: Routine surveillance activities (accumulated case reports). Striking clustering of cases may suggest emergence of new diseases or epidemics

Case report and case series

- **Clinician finds unusual features of a disease or effects of a drug, or the patient's medical history, that lead to the formulation of a new research question or hypothesis**

Stay strong

For example, as we discussed last time, Professor Howen described 20 cases of cervical cancer, 17 of which were HPV positive. Another example could be women using oral contraceptives, where two of them developed pulmonary embolism or were newly diagnosed with hypertension potentially secondary to these contraceptives. Such unusual findings can be documented as a case series.

We also provided the classical example of Professor Howen's work: he observed HPV-positive cases, conducted a cross-sectional study followed by a case-control study, and eventually proved that HPV is a risk factor for cervical cancer. He then conducted a clinical trial and won the Nobel Prize. This illustrates that, as a clinician in your clinic, you can make a big difference.

Consider clinical trials, for example. Suppose we have a new treatment for hypertension, and a clinical trial is conducted with 300 participants receiving the new treatment and another 300 receiving the standard treatment. If the new treatment proves to be superior and has fewer side effects, you might start using it for your patients and eventually across all patients with hypertension in Jordan

However, imagine that this new treatment has a renal impairment side effect occurring in one per thousand or one per 10,000 patients. When you start administering this medication to a larger population, say 10,000 or 100,000 patients, you may begin to observe cases of renal impairment. As a physician, it's crucial to share these new cases of renal impairment.

In such situations, you might employ what is known as the "challenge and re-challenge" hypothesis: you stop the new medication, return patients to the previous one, and observe if renal function improves. If it does, this indicates that the new medication could be causing the adverse reaction. Sharing these findings through a case series with other physicians can build enough evidence to consider removing this medication from the market.

Even if the incidence rate is only one per thousand, this could result in a high number of patients with renal failure due to the medication when millions are treated annually. This side effect may not have been visible in the clinical trial due to the low incidence rate (one per thousand, one per 10,000, etc.), which highlights why case reports and case series are essential. They allow us to observe and share rare but important outcomes, enabling better decisions on medication safety.
So, whether you present a case report or a case series, these reports are invaluable for advancing medical knowledge.

Hammade et al.
Journal of Medical Case Reports (2022) 16:386
https://doi.org/10.1186/s13256-022-03630-1

Journal of
Medical Case Reports

CASE REPORT

Open Access

Isolated giant renal hydatid cyst with a simple renal cyst appearance: a case report

Mohammed Hammade[1*], Sami Alhoulaiby[1] and Adnan Ahmed[2]

Please read the paper

Abstract

Background: Isolated renal hydatid cysts of the kidney are a rare occurrence that account for about 2–3% of all hydatidoses. They can stay asymptomatic for years and could have a variable presentation on imaging techniques, which results in a challenging diagnostic process.

Case presentation: We report a 22-year-old Caucasian male with a large cyst on the upper pole of the left kidney that had no septations nor membrane calcifications on computed tomography, which led to mistakenly considering it a simple renal cyst. The true diagnosis was identified intraoperatively and proven postoperatively by pathology.

Conclusions: This case highlights the importance of keeping echinococcosis in mind when treating suspected renal cysts and tumors to avoid incorrect treatment and possible content spillage, anaphylaxis, and peritoneal dissemination.

Keywords: Isolated renal hydatid cyst, Renal echinococcosis

Case Reports Case Rep Neurol
. 2017 Mar 20;9(1):44-48. doi: 10.1159/000460814. eCollection 2017 Jan-Apr.
A Case Report of Severe Delirium after Amantadine Withdrawal
Franz Marxreiter 1,
Jürgen Winkler 1, Martin Uhl 2, Dominik Madžar 2 Affiliations expand
PMID: 28611642 PMCID: PMC5465776 DOI: 10.1159/000460814
Free PMC article
Abstract
Amantadine is frequently used in addition to dopaminergic substances like dopamine agonists or L-Dopa in advanced Parkins disease (PD). However, adverse effects like hallucinations limit its use. PD patients developing severe psychotic symptoms upo treatment with either dopaminergic substances and/or amantadine need to stop intake of any psychotropic substance. Here, report the case of a 71-year-old PD patient without previously known cognitive impairment. He presented with drug-induced psychotic symptoms due to changes in his therapeutic regimen (increase in COMT inhibitors, newly introduced MAO B inhibit Also, amantadine had been part of his long-term medication for more than 2 years. The severity of his psychotic symptoms required a L-Dopa monotherapy. After changing his medication, the patient developed severe delirium that resolved rapidly a
i.v. amantadine infusion, suggesting an amantadine withdrawal syndrome. Amantadine withdrawal syndrome is a rare advers event that may present even in PD patients without cognitive impairment. This case report highlights the need for a gradual withdrawal of amantadine even if acute and severe psychotic symptoms are present. Moreover, this is the first report of a cognitively unimpaired patient developing an amantadine withdrawal syndrome.

Keywords: Amantadine; Amantadine withdrawal; Delirium; Parkinson disease; Psychotic symptoms.

The classical thing that we practice in the fourth, fifth, and final years is that we take a history, perform an examination, and conduct investigations. Please note that we need to start with an introduction about the disease and the medication, report any side effects, and present your case. Then, we'll have a discussion about the manifestations, previous studies, and recommendations based on your study.

Case Reports Transpl Int
. 2002 Jul;15(7):374-6. doi: 10.1007/s00147-002-0426-9. Epub 2002 Jun 20.

Colchicine myoneuropathy in a renal transplant patient

Peter Dupont 1, Ian Hunt, Lawrence Goldberg, Anthony Warrens
Affiliations expand

PMID: 12122515 DOI: 10.1007/s00147-002-0426-9

Abstract
Colchicine is widely employed for the treatment of gout in renal transplant patients where NSAIDs are contra-indicated and allopurinol prophylaxis is often avoided due to concomitant azathioprine immunosuppression. We report here a case of colchicine-induced myoneuropathy in a renal transplant recipient. Our patient had myalgia, muscle weakness, elevated creatine kinase levels, myopathic changes on electromyography and peripheral neuropathy. Withdrawal of colchicine resulted in recovery within 4 weeks. Renal transplant recipients are likely to be at greater risk of colchicine-induced myoneuropathy due to the unique concurrence of risk factors predisposing to toxicity in such patients. These risk factors include the high incidence of gout in this population, widespread use of colchicine as first-line therapy, impaired renal function and concomitant cyclosporin treatment. The diagnosis should be considered in any renal transplant recipient receiving the drug who develops myopathy. Prompt withdrawal of colchicine therapy should result in rapid clinical and biochemical improvement.

Case reports

When you open any medical textbook, you'll find the case definitions of diseases along with their symptoms and signs. All of this information originally came from case reports in the 1940s, 50s, 60s, 70s, and earlier. In those days, there were fewer medications available, so patients often presented with more severe symptoms and signs. Physicians documented these presentations in various case reports and case series, which became the basis for understanding the symptoms and signs of diseases.

- The most common type of study published in the medical literature.
- They note unusual medical occurrences, identify new diseases, and describe adverse effects from drug therapies.
- Clinical investigators can use challenge–rechallenge data to help establish causality.
- In this approach, administration of a drug (the challenge) might be suspected of producing a specific symptom (side effect or adverse reaction).
- Administration of the drug can be stopped to observe whether the side effect or adverse reaction diminishes.
- If it does, then administration of the drug can be resumed (the rechallenge) to observe whether the effect returns, suggesting a possible relationship between the two events.

This is the challenge-rechallenge approach we mentioned. In clinical trials, we typically test medications on 500 to 1,000 patients, but the incidence of adverse reactions might be as low as one per 10,000. This is why we need to be vigilant and report these adverse reactions, especially serious ones, in case reports. For example, we could present five complicated surgeries conducted at our center. Or, if we have 20 cases of congenital heart disease at Jordan University Hospital, we could share the manifestations of these cases.

Case-series: Clinical case series

- Usually a coherent and consecutive set of cases of a disease (or similar problem) which derive from either the practice of one or more health care professionals or a defined health care setting, e.g. a hospital or family practice.

A clinical case series is a special type of case report. It typically involves a coherent, consecutive set of cases with a similar problem, and we follow up on these cases over time. In cohort studies, we compare risk factors, but clinical case series are a specific part of case reports. In our hospital, Jordan University Hospital, we have a registry for coronary heart disease, which contains all the relevant information about the patients. We follow these cases to examine the complication rates and quality of life.

Clinical Neurology and Neurosurgery
Volume 99, Issue 4, December 1997, Pages 266-270
Clinical Neurology and Neurosurgery
Case report
Acute onset of colchicine myoneuropathy in cardiac transplant recipients: case studies of three patients Author links open overlay panel Sandeep S Rana a, Michael J Giuliani a, Chester V Oddis b, David Lacomis a c Abstract
Colchicine causes both muscle and peripheral nerve toxicity of subacute onset in patients with renal insufficiency. We report three cardiac transplant recipients, treated with colchicine for cyclosporin A (CyA)-induced gout, who developed acute weakness due to colchicine myoneuropathy. The onset of disabling weakness occurred over a 1–2 week period.
All three patients had concomitant renal insufficiency and an elevated serum creatine kinase and two had elevated CyA levels at the time of presentation. Electromyography revealed features of myopathy and motor axonal neuropathy in all three patients. Two underwent muscle biopsy which confirmed the presence of sarcoplasmic vacuoles characteristic of colchicine-induced myopathy. All patients rapidly improved with either colchicine dose reduction or drug discontinuation. In conclusion, cardiac transplant recipients treated with CyA and colchicine may be at increased risk of developing colchicine-induced myoneuropathy especially in the setting of concurrent renal insufficiency. In patients with post-transplantation gouty arthritis, other treatment modalities are suggested; and if colchicine is administered, the dose should be reduced, CyA levels should be monitored closely and patients should be assessed for signs of neuromuscular toxicity.

We conducted a challenge-rechallenge, and all patients rapidly improved with either colchicine reduction or discontinuation. This is what we need to know. In conclusion, heart transplant recipients treated with colchicine and cyclosporine A may be at increased risk of developing myoneuropathy. This is something we can avoid in future patients.

Dehneh et al. Journal of Medical Case Reports (2022) 16:371
https://doi.org/10.1186/s13256-022-03609-y

Journal of
Medical Case Reports

CASE REPORT Open Access

Syrian females with congenital adrenal hyperplasia: a case series

Nada Dehneh[1*], Rami Jarjour[2,3], Sahar Idelbi[4], Assad Alibrahem[4,5] and Sahar Al Fahoum[1]

Abstract

Background: One of the most common types of congenital adrenal hyperplasia is an autosomal recessive disorder with 21-hydroxylase deficiency. The classical form, defined by cortisol insufficiency, is accompanied by prenatal androgen excess causing variable masculinization degrees of external genitalia in babies with a 46, XX karyotype.

Cases presentation: These five case reports highlight the management of Syrian females aged between 0 and 32 years with congenital adrenal hyperplasia. Two of the patients have been raised as males, while two had reconstructive surgery and one had hormonal therapy. Becoming mother was achieved by two patients

Conclusion: The integrated treatment of females with classical congenital adrenal hyperplasia CAH, which includes appropriate surgical procedures and controlled hormonal therapy, gives these females the opportunity to live as they are, and perhaps as mothers in the future.

Keywords: Congenital adrenal hyperplasia, Syria, Case report

Case-series: Clinical case series

- A case-series is, effectively, a register of cases.
- Analyse cases together to learn about the disease.
- Clinical case-series are of value in epidemiology for:
  - Studying symptoms and signs
  - Creating case definitions
  - Clinical education, audit and research

When we have a registry for patients with congenital heart disease or any other illness included in your study, for example, rare diseases where the number of cases is small, having a registry allows us to include them in clinical trials. We can follow them up to study and understand the natural history of the disease in these patients.

Case series:
Natural history and spectrum

- **Helps professionals can build up a picture of the natural history of a disease**

For cystic fibrosis patients, we can study the development of cognitive function improvement. Although there is no cure for the disease yet, we can observe the progression and follow these patients to understand the natural history of the disease, its outcomes, and how we can improve those outcomes.

Case series:
Natural history and spectrum

- **Population case-series is a systematic extension of this series but which includes additional cases,**
  e.g. those dying without being seen by the clinicians.

- **Add breadth to the understanding of the spectrum and natural history of disease.**

Case series: Limitations

Usually we cannot estimate the prevalence or incidence rate

- **Breast cancer registry in Jordan: We cannot provide prevalence rates without:**

1. **Population size**
2. **Time- period of data collection**
3. **All cases of breast cancer are registered**

Exception for calculation of the incidence: Jordan National Cancer registry can generate data on the incidence.

All cancer cases in Jordan are reported to the Registry office.

No control group for comparison

When you have 20 congenital heart disease patients at Jordan University Hospital, we can't calculate the incidence or prevalence accurately because there are other patients at the Royal Medical Service, the Ministry of Health, and in the private sector. This is the main limitation: we can't estimate the prevalence or incidence. Another limitation is that there is no control group for comparison.

For example, we have 20 cervical cancer patients who are HPV positive. It may be that HPV positivity is high in that community, and when we compare this to the general population, we find a prevalence of 70%. This means there is no significant difference (70% - 70%).

If we want to compare, for example, hypothyroidism and smoking, we have 20 hypothyroid patients, 15 of whom are heavy smokers. When we look at heavy smoking among the general population or a matched control group, we may find similar numbers, such as 14 or 16. Therefore, we can't actually calculate the prevalence or incidence. These case series are good for generating hypotheses, but they are not suitable for understanding the magnitude of the problem. We need a control group to compare our results.

The main limitation is that we can't calculate the incidence. However, there is one exception: we can calculate the incidence in a case series if we have data from the whole country. For example, if we want to study congenital heart disease in Al-Karak, and we include data from all hospitals (military, private, and Ministry of Health), we may be able to calculate the incidence. However, if many pregnant women at risk give birth in Amman, we can't calculate it accurately.

But if there is a law that mandates the reporting of any case of congenital heart disease born in Jordan to the Ministry of Health, then we would know about all cases in the country, and we could study the incidence. This actually happens in Jordan with the cancer registry. Since 2003 or 2004, all cases of cancer must be reported to the Ministry of Health from all hospitals (private, public, military), laboratories, etc., by law.

So, if we have, for example, 5,000 new cancer cases across the country, we can calculate the incidence by cancer type for all cancers, compare different age groups, and analyze regional differences (north, middle, south of the country). This is the exception, when we have a legal mandate that ensures all cases are reported.

As a general rule, case series are not good for calculating prevalence or incidence because we don't know about all the other cases. The only exception is when all cases in the country are included, so we can accurately calculate the incidence.

I'll give you an example: in 1997, the Jordan Cancer Registry started. Initially, it only had data from Al-Basher Hospital. Two years later, they started including data from Ministry of Health hospitals, and after that, from the Royal Medical Services and the private sector. If I want to compare the incidence of breast cancer in 2022 with previous data, I should not compare it with 1997. In 1997, there were only 300 cases of breast cancer. If I compare it with 2022, where we have 2,000 new cases, it would seem like the incidence has increased by 30 times, which is incorrect. I also shouldn't compare it to the year 2000, when only Ministry of Health hospitals were included, as we would be missing the private and military sector
patients.
The correct comparison would be with the year 2004, when all sites in Jordan were required by law to report their cancer cases, including hospitals and laboratories. Therefore, I should compare the 2,000 cases in 2022 with the 1,000-2,000 cases in 2004, as this would be a more accurate comparison. It's a common mistake to say that the incidence increased from 300 cases in 1997 to 3,000 cases in the current year, as this is not correct. We can only calculate the incidence when we are confident that all sites in the country are included.

Case series: Population

- **Case-series** can provide the key to sound case control and cohort studies and trials
- **Design of a case-series is conceptually simple**
- **Defines a disease or health problem to be studied and sets up a** system for capturing data on the health status and related factors in consecutive cases

Congenital Rubella Syndrome: The classic description of a series of infants born with congenital cataracts, some with additional cardiac abnormalities, in Australia in 1941.

This led Gregg in Sydney to postulate a causal link between a severe epidemic of rubella that had occurred six to nine months before the children were born and the subsequent abnormalities.

It is now well known that if a woman develops rubella during pregnancy it may affect her unborn baby.

Dehneh et al. Journal of Medical Case Reports (2022) 16:371
https://doi.org/10.1186/s13256-022-03609-y

Journal of
Medical Case Reports

CASE REPORT Open Access

Syrian females with congenital adrenal hyperplasia: a case series

Nada Dehneh[1*], Rami Jarjour[2,3], Sahar Idelbi[4], Assad Alibrahem[4,5] and Sahar Al Fahoum[1]

Abstract

Background: One of the most common types of congenital adrenal hyperplasia is an autosomal recessive disorder with 21-hydroxylase deficiency. The classical form, defined by cortisol insufficiency, is accompanied by prenatal androgen excess causing variable masculinization degrees of external genitalia in babies with a 46, XX karyotype.

Cases presentation: These five case reports highlight the management of Syrian females aged between 0 and 32 years with congenital adrenal hyperplasia. Two of the patients have been raised as males, while two had reconstructive surgery and one had hormonal therapy. Becoming mother was achieved by two patients

Conclusion: The integrated treatment of females with classical congenital adrenal hyperplasia CAH, which includes appropriate surgical procedures and controlled hormonal therapy, gives these females the opportunity to live as they are, and perhaps as mothers in the future.

Keywords: Congenital adrenal hyperplasia, Syria, Case report

Disease registry

Definition of Registry

- The term *registry* is defined both as the act of recording or registering and as the record or entry itself.
- Therefore, “registries” can refer to both programs that collect and store data and the records that are so created.
- **Special form of case series**

I want you to understand what a registry is. It is a special form of a case series. We collect data in a registry for patients with inflammatory bowel disease, for example, or certain cancers. All patients who come to these sites are included in the registry. We have information about their symptoms, signs, investigations, treatments, and we perform follow-ups. This allows us to look at complication rates and quality of life. These factors are valuable for understanding the patients and what is happening to them, so we can improve outcomes and reduce complications. Additionally, we can include these patients in clinical trials. With the data we have, we can gain insights into the situation of diabetic patients in Jordan, the situation of cystic fibrosis patients, and so on.

Webster's English Dictionary. [August 12, 2012]. http://www.m-w.com.

Disease Registry

- Patient registries have been defined as:

"an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves a predetermined scientific, clinical, or policy purpose(s)."

We do not intervene in the registry; it simply includes patients who come to seek medical treatment at your site. After obtaining their consent, they are included in the registry, and we perform follow-up for them and collect their data. This provides valuable scientific and clinical information. We can use this data to assist in policy-making. For example, we can compare the outcomes of patients receiving a particular treatment to those receiving different treatments, without the need for a clinical trial. For instance, if the Royal Medical Services are using a treatment different from the one at Jordan University Hospital, you can compare the outcomes using the registry data.

https://patientregistry.ahrq.gov.

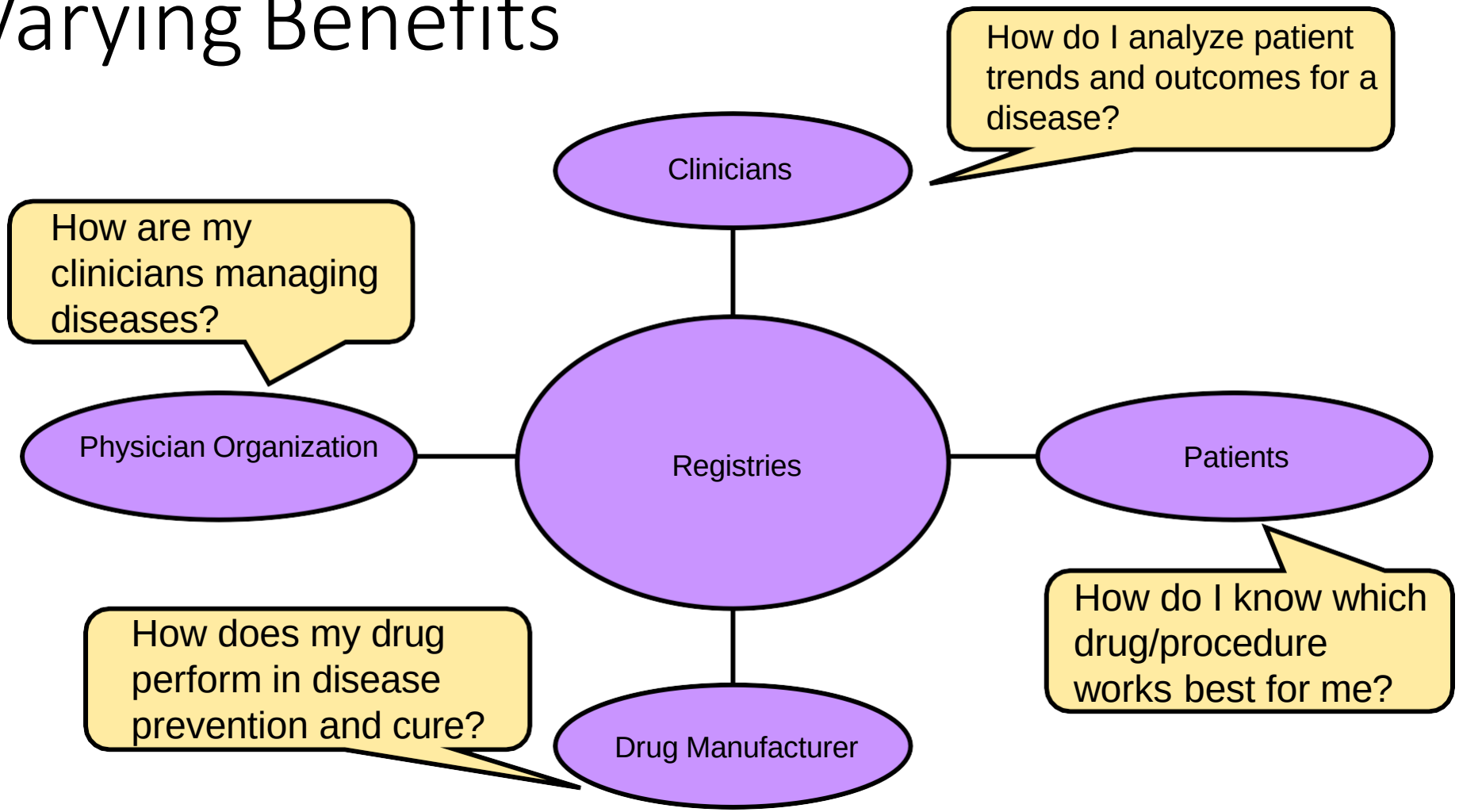
Traditional Patient Registries

- The purposes for patient registries can range widely.
- According to the National Institutes of Health:
- "Registries can be used to recruit patients for clinical trials, to learn about a particular disease or condition; to develop therapeutics or to learn about population behavior patterns and their association with disease development; developing research hypotheses; or for improving and monitoring the quality of health care."

I have the registry of patients with Gaucher disease/cystic fibrosis. I make follow-up for them and advise them to take part in the clinical trial. I know them, and I have the pool there ready for the clinical trials. Actually, in the UK, the registry for rare diseases is a huge thing to help patients. You have these patients taking part in clinical trials for potential treatments that will help them and receive the standard treatment versus the new treatment. It has a great impact on the patients, improving scientific knowledge, and also has a good financial impact for the organization

Rubinstein Y. Patient Registries. [Accessed March 1, 2013]. http://rarediseases.info.nih.gov/PatientRegistry.aspx. [Reference

Varying Benefits



NO clinical trial, Just comparing

Real World Evidence Analysis

- Customized Real World Evidence Analysis: Application and treatment results of various drugs in clinical routine

- **REAL WORLD EVIDENCE** Analysis – Analysis of defined patient cohorts under “real life” conditions (including all comorbidities, AEs & SAEs incl.)

I want to conduct a clinical trial to control diabetes. I will have many inclusion and exclusion criteria, and these patients will be specific to the trial. They may differ from patients in regular treatment, as they might have different illnesses, such as liver or renal function impairments, or other conditions. There are different factors in the clinical trial setting that might differ from real-world evidence. This is why we need registries.

In a registry, we are giving patients these medications and can assess the impact and compare the outcomes. The advantage of a registry is that, for example, if you have a new novel treatment for cancer, such as breast cancer or lung cancer, used in a multicenter, randomized clinical trial across different countries, you may not have that trial conducted in Jordan.

If I accept the results of a large, randomized, multicenter clinical trial, and I begin giving this treatment to my patients, I may observe that the incidence of side effects and adverse reactions is much higher among Jordanian patients compared to others. This suggests that there might be something wrong, such as our patients needing a lower dose, or perhaps this medication is not suitable for them. Without a pool of patients to analyze and compare data, we cannot accurately assess the outcomes.

There are hundreds or even thousands of new medications and treatments coming through the pipeline, but unfortunately, participation from the Middle East in clinical trials is very limited. The only way for us to evaluate the impact of these interventions, which we have already started using based on data from outside, is through real-world evidence and registries.

Quality Improvement

- How do we know a change is needed?
- How do we know a change is an improvement?
- How do we know where to put scarce resources?

A Disease Registry can provide data to:

- Describe the patient population
- Identify patient sub-groups having the most need
- Identify who is in the sub-groups
- Show the ‘reach’ of intervention programs
- Show the outcomes of intervention programs
- Pharmacovigilance: supports reporting of ADRs

A registry is a case series; it is observational. We are not providing any intervention based on the registry. In a registry, you have a group of patients that you can include and invite to participate in a clinical trial, but here we are simply describing what they are receiving. I am just observing; there is no intervention. We can look at adverse drug reactions based on that.

Types of Registries

- Mortality registry
  - An important thing to know about your patients
- Research Patient Registry
  - Clinical Trials
- Disease or Condition Registries
  - Disease or condition registries use the state of a particular disease or condition as the inclusion criterion.
  - One disease or group of diseases: Cancer registry, multiple sclerosis registry, bleeding disorders.
- Service, intervention, device registry

BMT registry, Biosimilars registry

Coverage

- Hospital or clinic based: Do not use for calculating incidence Only if you know all cases
- Local
- Regional
- National: Excellent for calculation of incidence if there is a valid and reliable surveillance system in place.
- International

Question for discussion: how can we collect data for the above types of registries?

Registries VS. RCT's

- RCT
  - Best for assessment of therapeutic efficacy
- Registry (observe the outcomes)
  - Therapeutic effectiveness
  - Safety/harm of therapy
  - Generalizability to populations
- Key Difference
  - Registries do not randomize

Note:
Efficacy vs effectiveness

Ho, Circulation 2008, 1675-84

Uses for Patient Registries

- To observe the course of disease (natural history)
- To understand variations in treatment and outcomes
- To examine factors that influence prognosis and quality of life
- To describe care patterns, including appropriateness of care and disparities in the delivery of care
- To assess effectiveness
- To monitor safety

I have breast cancer survivors, and I will do a follow-up to look at the factors that can affect survival, such as quality of life, depression scale, and adverse drug reactions. We can assess all of these things in the registry. We can also describe disparities; for example, in some centers, you might find all treatments available according to the NCCN oncology guidelines, while in other centers, they might not be available. By having the registry, we can address these disparities in management by looking at outcomes and therapeutic options at each site.

Components of disease registry

- Personal Domain
- Exposure Domain
- Outcomes Domain

We can look at the personal characteristics of subjects, as well as the treatment they receive, including doses, intervals, etc., and the outcomes we are assessing, such as clinical outcomes, quality of life, complications, etc.

The personal domain

- Consists of data that describe the patient, such as information on patient demographics, medical history, health status, and any necessary patient identifiers.

The exposure domain

- Describes the patient's experience with the disease, medication, device, procedure, or service of interest to the registry.
- Exposure can also include other treatments that are known to influence outcome but are not necessarily the focus of the study, so that their confounding influence can be adjusted for in the planned analyses.
- Baseline assessment and storage of samples

Sometimes we have something called a biobank, which provides a baseline assessment and stores samples. However, this should only be done after obtaining the patient’s consent to look at future predictors.
Currently, we face major challenges in the management of different illnesses, such as cancer. With the advent of precision medicine and immune therapies, we want to identify different predictors of outcomes. Biomarkers are continuously changing, so we need to collect baseline samples and store them at -80°C, for example, to analyze the results later. However, it is crucial to have a consent form from the patient before collecting these samples.

The outcomes domain

- Consists of information on the patient outcomes that are of interest to the registry (survival, disease control, complication rate)
- This domain should include both the primary endpoints and any secondary endpoints that are part of the overall registry goals.

Current Trends Measuring Quality Using Registries

- Quality-focused registries are being used increasingly to assess differences between providers or patient populations based on performance measures that compare:
  - Treatments provided or outcomes achieved with “gold standards” (e.g., evidence-based guidelines)
  - Comparative benchmarks for specific health outcomes (e.g., risk-adjusted survival or infection rates)

- Role of health information systems

Now, we have the AHS system in Jordan and in different countries, such as Hakeem in Jordan, where we have various databases. We can collect data from these registries, but we need to ensure that, at baseline, we have all the necessary information for the registry. We can ask our colleagues from the IT department to edit the patient profiles or data for specific illnesses. For example, if we are working with congenital diseases or diabetes, we will ask them to add more items to the database to ensure that we are including all the necessary information in our registry.

Quality Management Reporting - Example

	Eligible	Satisfied	Rate
Preventive Services			
Cervical Cancer Screen	223	146	65%
Mammogram	138	83	60%
Colorectal Cancer Screen	355	143	40%
Pneumonia Vaccine	144	33	23%
Osteoporosis Screened or on Treatment	75	44	59%
Cardiovascular Disease			
HTN: good BP control (mean or last <= 140/90)	310	196	63%
CAD: antiplatelet medication	62	54	87%
CAD: lipid lowering medication	65	54	83%
CAD: Beta blocker post-MI	12	10	83%
CAD: ACE/ARB if DM or LVSD + CAD	25	19	76%
CHF: anticoagulation for AF + HF	6	5	83%
CHF: ACE/ARB if LVSD	3	3	100%
CHF: beta blocker if LVSD	3	3	100%
Diabetes			
Last Hba1c <= 7	87	37	43%
Last Hba1c <= 9	87	66	76%
Good BP control (mean or last BP <= 130/80)	83	39	47%
Good LDL control (<100)	87	49	56%
Nephropathy: screened or on ACE/ARB	87	64	74%

Yancy B, Royalty JE, Marroulis S, Mattingly C, Benard VB, DeGroff A. Using Data to Effectively Manage a National Screening Program. *Cancer*. 2014;120(0 16):2575-2583.

Getting the Most Out of Your Disease Registry

- Cost effective & treatment efficacy
- Feedback reports to physicians about their care practices
- Process improvement projects for service line clinical programs
  - Use trend analysis to find possible process deficiencies that affect patient care
- Population reporting and analysis for research (e.g. Epidemiology)

You can compare the cost-effectiveness of different interventions through the registry, as they provide real-world data. We actually conducted a study in the country on S. pneumonia serotypes, where we looked at the cost of treatment and compared it with the outcomes of the vaccine. These registries are very useful, especially in Jordan, with platforms like Hakeem, and in the UK with systems like Vist (I'm not sure if I spelled it right). From these registries, we can study the cost-effectiveness of different interventions, the burden of various illnesses, and compare them with preventive measures.

To conclude, a registry is a special type of case report or case series, where we follow patients over time. In these series, we look at different outcomes and compare the data with the patient's disease and its outcomes. We do not provide any intervention in a registry; it is an observational study. If I want to change the treatment, modify a dose, or stop medication, I would need to conduct a clinical trial. In a registry, I am just observing what is happening. Real-world evidence is incredibly valuable as it provides insights into health outcomes, disease patterns, and even pharmaco-economics or health economics of different interventions. We can compare data from different sites and assess the outcomes.

Thank you very much. 😵‍💫 🌠 😵‍💫 🌠

شكوت إلى وكيع سوء حفظي فأرشدني إلى ترك المعاصي
وأخبرني بأن العلم نـــــــور ونور الله لا يهدى لعاصي

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!