

Cohort Event Monitoring

a description of the methodology and a tool to support it

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Pharmacovigilance methods

Spontaneous reporting

- The most common way of performing pharmacovigilance today
- Reports (ICSRs) are “spontaneously” arriving from different sources like physicians or companies
- Describes a possible Adverse Drug Reaction (ADR) or Adverse Event Following Immunization (AEFI) caused by a drug or vaccine.
- Report data stored in local databases but also collected in the global WHO database - VigiBase



Analysis of patient records

- Extending pharmacovigilance 'tool kit' to analysis of longitudinal health care data
 - Existing datasets
- Data mining methods and prototype analysis tools already available in the UMC research and signal departments
- Based on patient record data
 - Method developed to work on different datasets (but with similar content)
 - Can be adapted for more generalized datasets



Why is this not sufficient

- Drawback with spontaneous reporting
 - Long delay
 - Severe under reporting
 - No denominator data
- Drawback with patient record screening
 - Not available in many settings
 - Under recording of events
 - Those where medical care is not sought for
 - Usually not updated with information about vaccines



Cohort Event Monitoring

Cohort Event Monitoring

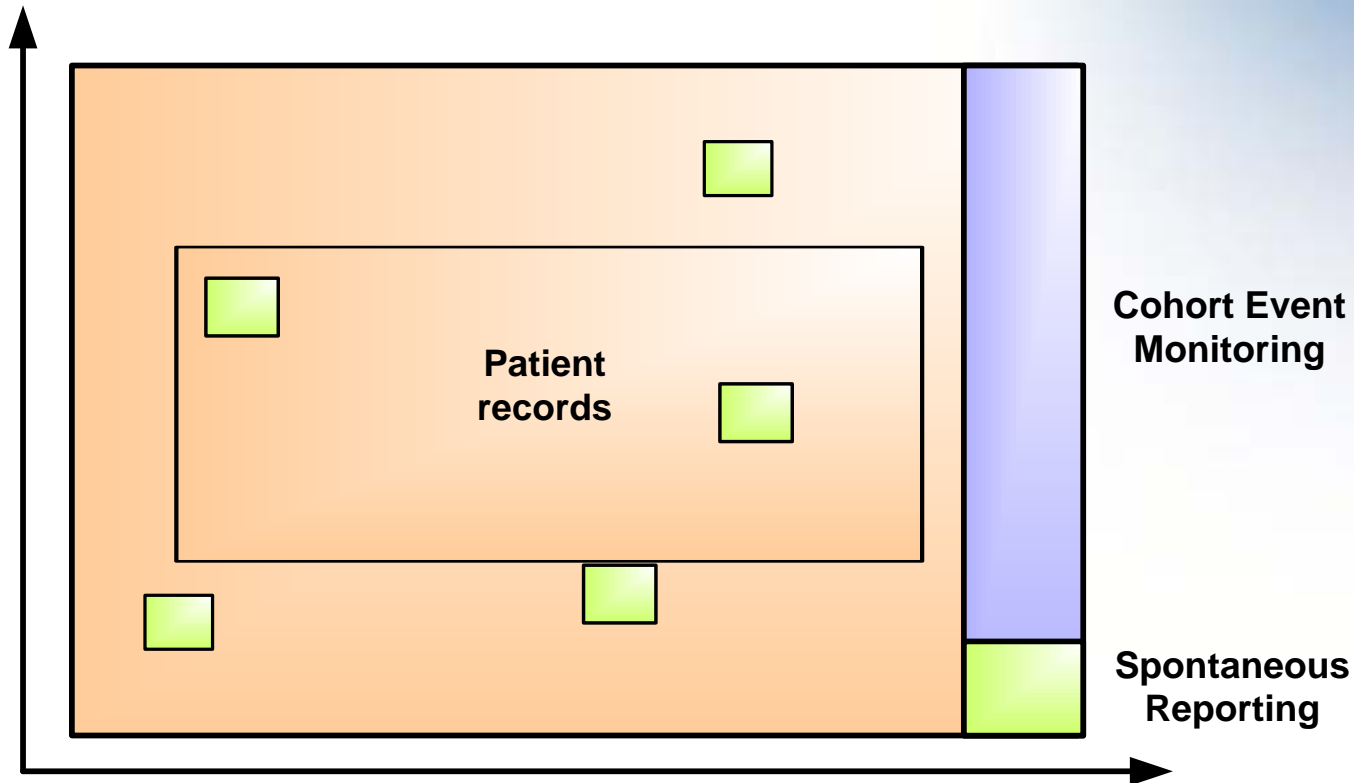
- The big difference from Spontaneous Reporting are:
 - Only one defined drug or group of drugs is monitored
 - (not any drug)
 - The data is collected in a systematic way
 - (not spontaneously)
 - All events are recorded
 - (not necessarily ADRs)
 - Data for all patients in a cohort is collected
 - (not only patients that suffer from an Event/ADR)
 - “Immediate” results
 - Not the “normal” delay as in Spontaneous Reporting



Different focus (simplified)

- Spontaneous reporting
 - Focus on ADRs/AEFIs
- Patient records
 - Focus on patients
- Cohort Event Monitoring
 - Focus on drugs/vaccines

Different perspectives



What about case control studies

- Powerful when possible to use – for example in the development phase of a new drug but:
 - Not always possible to use in a real life scenario where a mass treatment or mass vaccination program is being performed
 - Unethical in a post marketing situation!
 - As we will see – a requirement on CEM is that it shall be observational and non-interventional



Cohort Event Monitoring – CEM –



Overall objective with CEM

- Achieve **maximum benefit,**
least harm, for the patient

Objectives

- Characterise known reactions
- Measure risk
- Detect signals of unrecognised reactions
- Detect Interactions
- Identify risk factors like Age, Gender, Dose...
- Assess safety in pregnancy and lactation
- Detect inefficacy

How is this accomplished?

- **Monitor** a specific drug or group of drugs by
 - Collecting:
 - All data
 - **Events**, patient details, concomitant medications...
 - For “all” patients
 - In the **Cohort**
 - Analyze
 - To get risk profiles and other statistical data
 - Produce recommendations

Cohort Event Monitoring



**What if one
was shot...?!**



Methodological principles

- Observational
 - Only observe patients under normal treatment
- Prospective
 - Define your cohort in advance
- Longitudinal
 - Collect data repeatedly during treatment – possibly also on a long term basis
- non-interventional
 - Do not interfere with normal treatment – except from collecting data via e. g. interviews
- Inceptional
 - Start monitoring when treatment begins



Methodological principles

- observational
- prospective
- longitudinal
- non-interventional
- inceptional



Remember that we are monitoring actual patients in a post marketing situation!!

Methodological principles

- In Cohort Event Monitoring (CEM) a group (cohort) of patients are monitored while treated with a specific drug (or group of drugs).
 - Collect data about the patients as complete as possible as they are enrolled
 - This will be the **denominator**
- **All events** in a control period **before** and **after** treatment shall be recorded.
 - As complete as possible
 - This will be the **numerator**



Selection of cohort

- The cohort should be picked without biases among “all” patients being treated.
 - For example, all patients visiting a clinic on Tuesdays and Wednesdays (being treated with the monitored drug)
- All patients, falling into the rules of the cohort setup, must be enrolled (*to avoid biases*)
- Continue the enrolment until the predefined size of the Cohort is reached



Events = reactions + incidents

- **Reactions**

- definite
- probable
- possible

- **Incidents (background noise)**

- unlikely
- Unclassified (conditional)

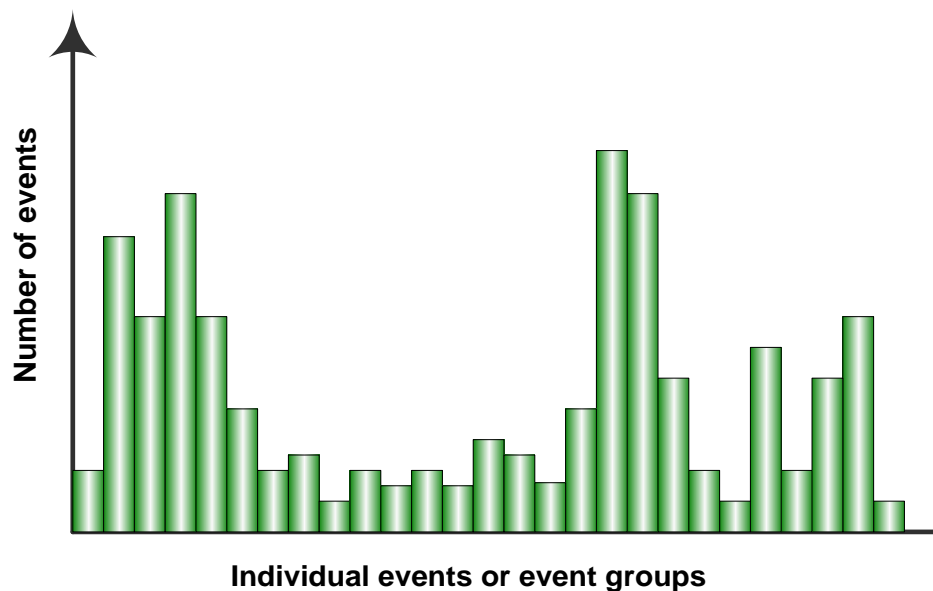


What to record

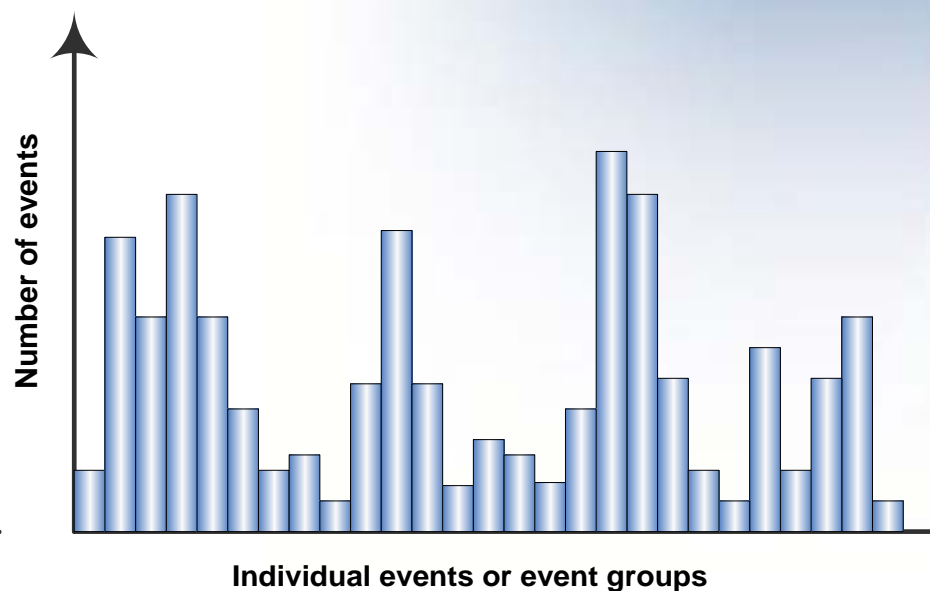
- All new **Events** even if common & minor
 - Change in a pre-existing condition
 - Abnormal changes in laboratory tests
 - Outcomes
 - Accidents
 - **All deaths** with date & cause
 - Concomitant medications
 - Concomitant diseases
 - Lost to follow up!!
 - ...
- Events = reactions + incidents**



Why collect events before and after

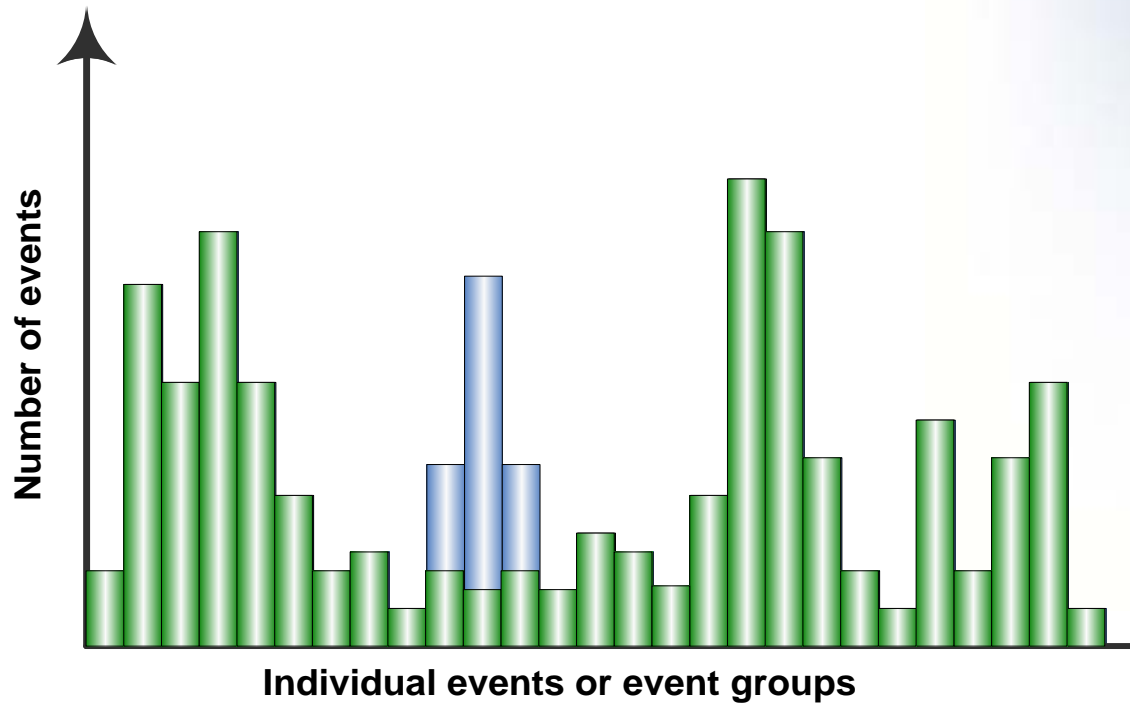


Events in the comparator period (before treatment)

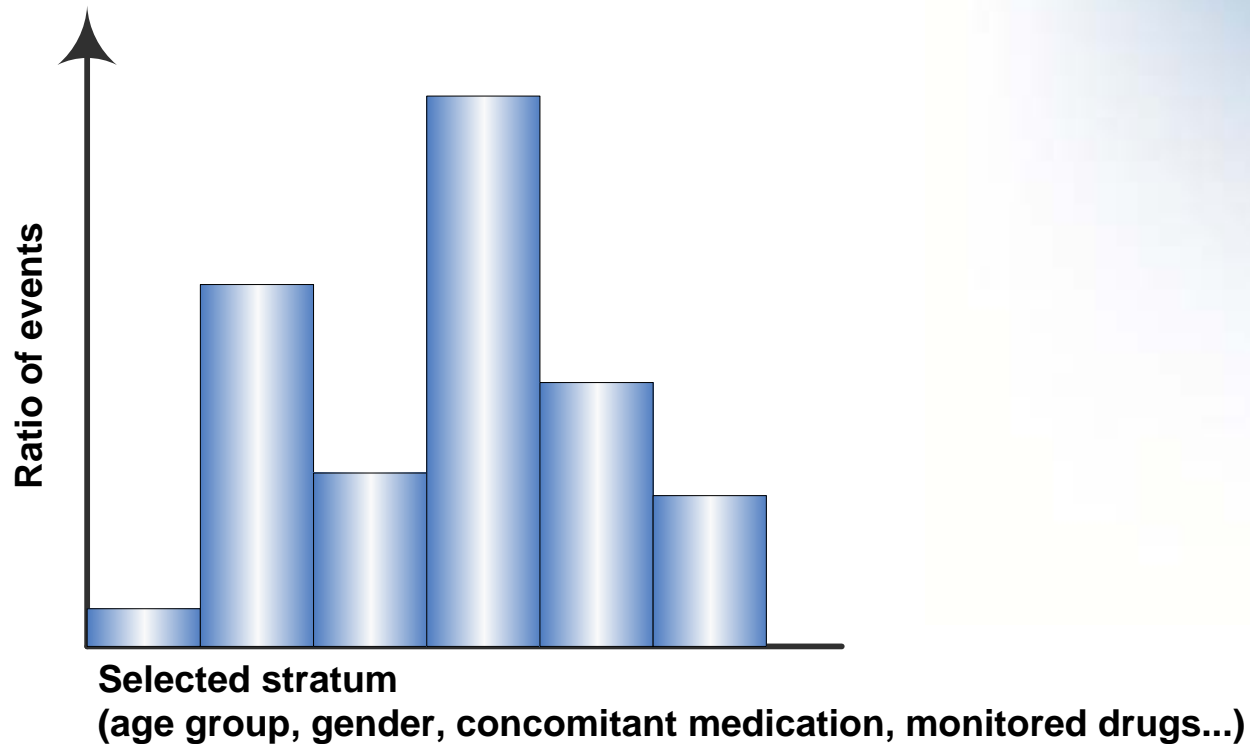


Events after treatment

Why collect events before and after



Stratification possibilities



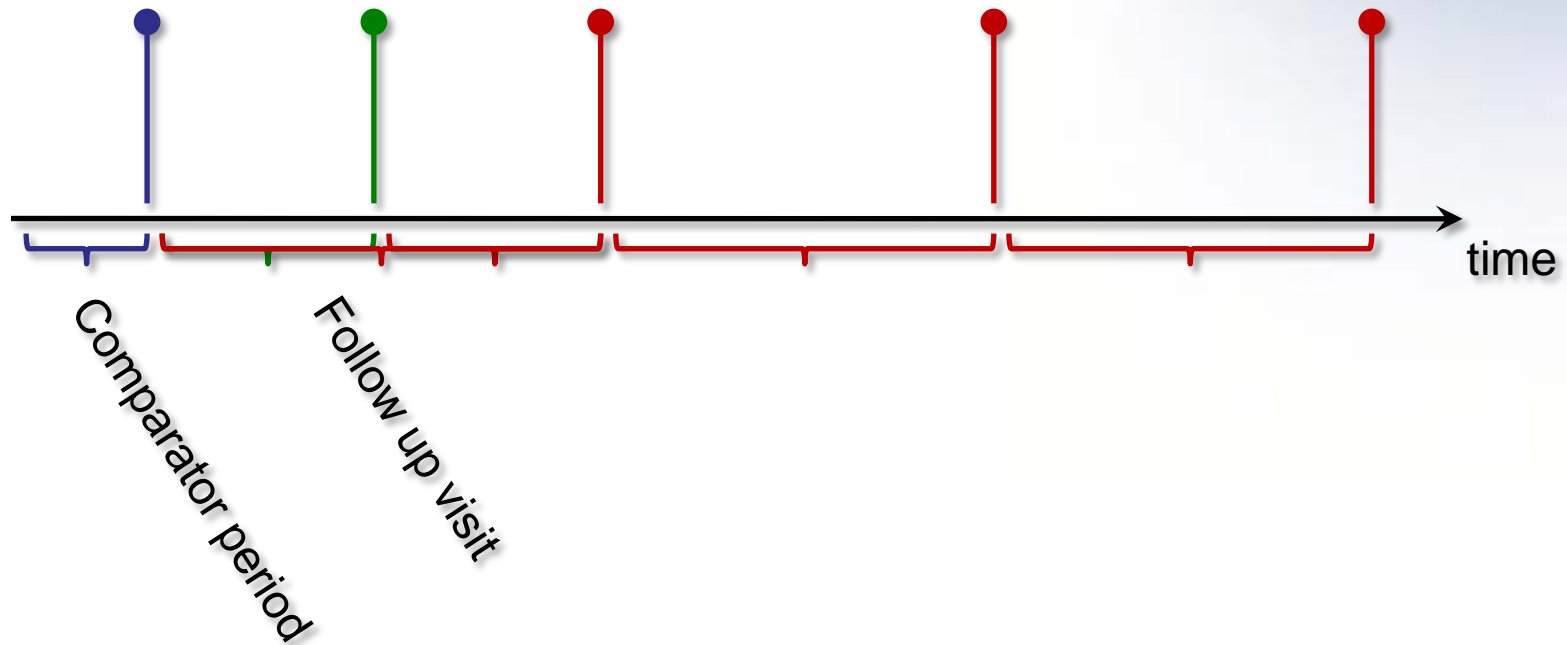
Challenges

- Follow up of patients
 - Easier if multiple treatment visits since follow up information can be collected at the next visit
- Coding of events
 - Must be done consistently so that the data can be analysed in a meaningful way
 - Some kind of event dictionary is required
 - It must be possible to add new events on a regular basis



Collecting the events...

(alternatives in long term monitoring)



What about CEM in the reality



How is this done in practice

- Data is collected in a number of pre selected sites
 - All personnel doing data collection must get an **understanding** of the method and training in how to collect the necessary data
 - It is crucial that the data is collected in a systematic and consistent way at all sites to simplify (*allow for*) analysis
 - Routines for patient follow up must be established
 - Completed forms shall be sent on a regular basis to the unit responsible for data entry (in e. g. CemFlow)
 - CemFlow can be used for data entry directly on the sites
 - CemFlow will be covered in details later



What about CemFlow

- Data shall be entered on a regular basis (as quickly as possible in CemFlow)
 - This might give early warnings about problems:
 - With the forms used for data collection
 - With the interpretation of the CEM methodology at the sites
 - *With the monitored medicine!!*
- If possible... the data entry into CemFlow can be done already by the interviewer or a dedicated CEM focal person at the site
 - **CemFlow is built for this purpose!!**



Analysis of the collected data

- A great benefit with prompt data entry into CemFlow is that up to date statistics can be easily produced
- Progress of the CEM program can be easily viewed by anyone with appropriate access rights
- The updated data can be used by e. g. the National Competent Authority in the day to day safety work
- *Early warnings on problems with the treatment can save patients from unnecessary harm*



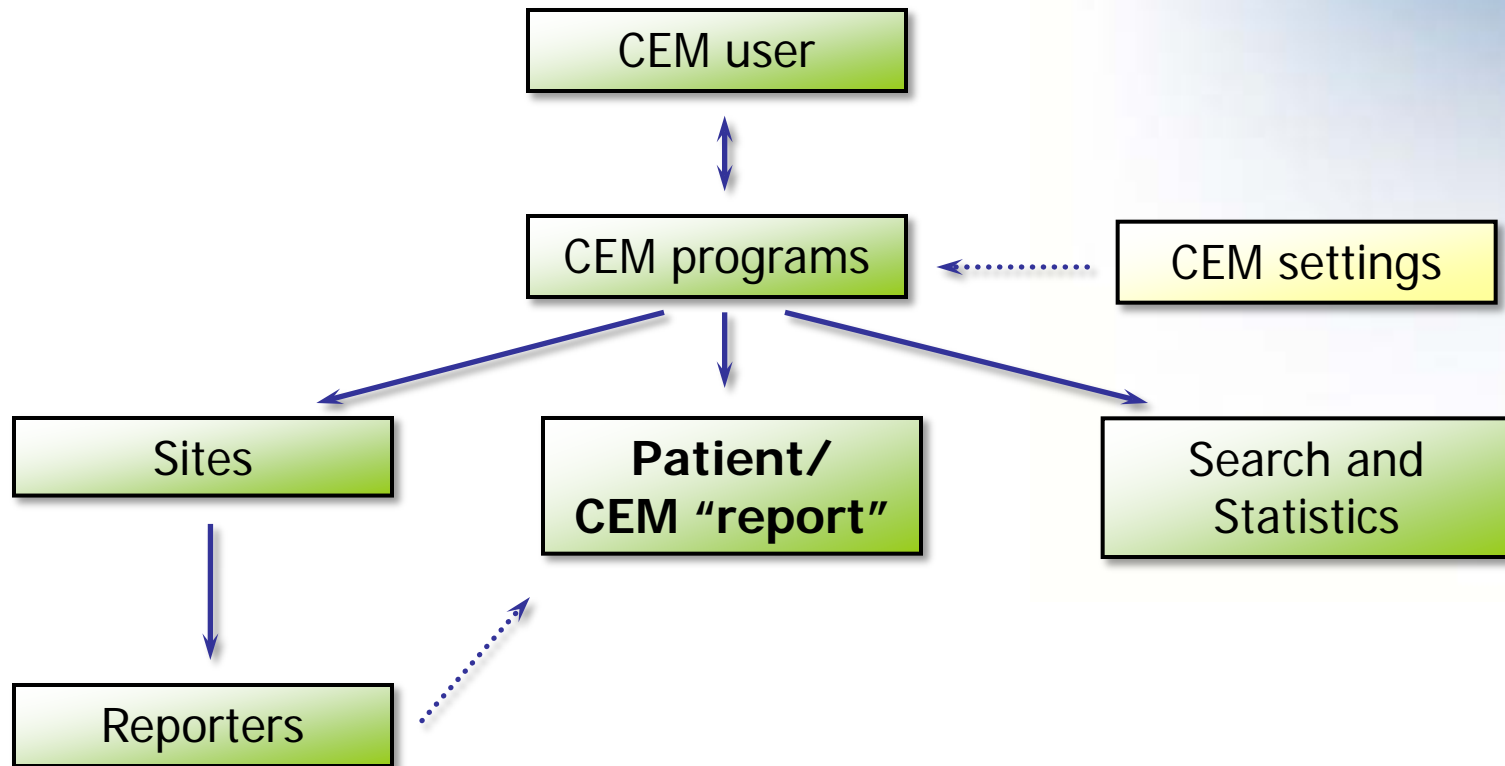
More about CemFlow

CemFlow

- CemFlow is a tool for:
 - Collection of CEM data
 - On central level as well as primary reporter level
 - Supports paper based data collection
 - Analysis of CEM data
 - Management of:
 - Users
 - Reporters
 - Sites
 - CEM programmes
 - CEM dictionary



CemFlow structure



Welcome to CemFlow

CemFlow is a tool designed for the purpose of collecting data originating from Cohort Event Monitoring programs. The tool has been built in cooperation between the World Health Organization and the Uppsala Monitoring Centre. It is based on data collection questionnaires that were developed and fine tuned jointly among a number of experts from different countries and with different experiences.

Available CEM programs

Please choose a Cohort Event Monitoring program from the list below in order to get started.

Cem Nigeria for Malaria (TEST)

Another program for Aspirin

New program 3

TFDA CEM program for Malaria (TEST)

Cem TFDA for Malaria upd

Cem ARV for WHO

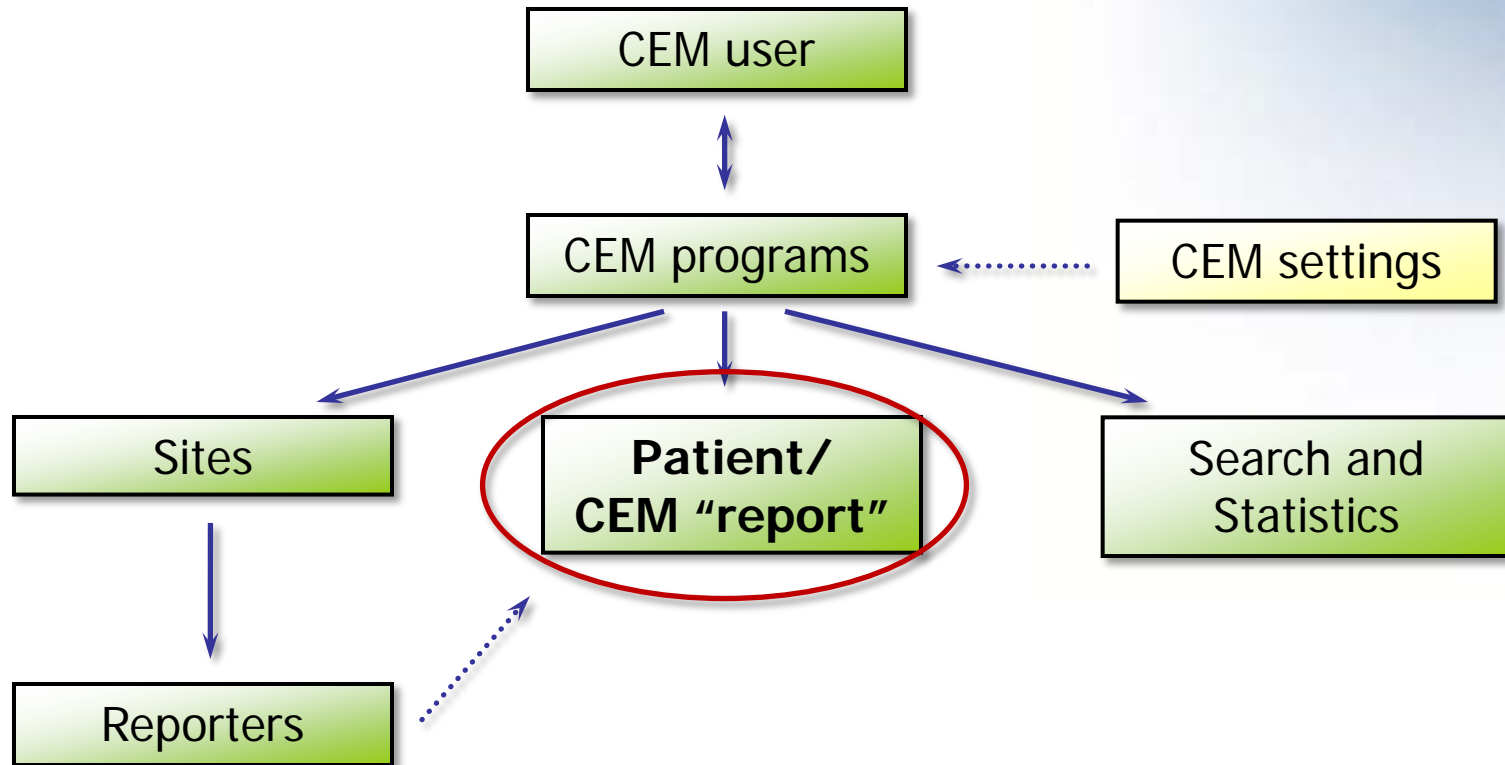
Test 110420

UMC demo 110517

We begin our detailed CemFlow tour with the actual data entry...



CemFlow structure



CEM “report” - patient

- A CEM “report” is the CemFlow equivalent to the CEM questionnaires but it can also be seen as the “patient”
 - All questionnaires for one patient are entered in one CEM report
 - One Treatment Initiation and any number of Follow Up questionnaires
 - The equivalent to an individual questionnaire is entered as a “visit” with the events as the most important information items
- CEM reports are managed through the Patient Data Entry module of CemFlow



List of patients/CEM reports

- To be able to access old patients/reports a patient list with a filter is the first view in the patient data entry area
- There are several reasons to open “old patients”
 - Adding additional information (about for example a follow up visit)
 - Doing an assessment
 - Viewing a specific report
- The CEM ID number is the easiest way of identifying a patient



CEM ID no. patient initials status

first name last name rows to display

We are in the "patient data entry" module



If you loose your internet connection – reports can be saved locally... this is where to find those!

Add a new patient here!


Indicates that a report has been assessed!

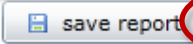
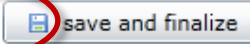

id	initials	birth date	sex	status	actions
60423			male		
00201			male		
ME			unknown		
1	AV	19910101	female		
123456	oo	19700101	male		
ABCDE	JK	19810101	male		
123456	oo	20010101	female		
213	ZMP1	19690201	female		
	CD	80617	female		
AA003	ccdd	19990828	female		
A00003	DC	19330813	male		
ABC123	OP	19800101	male		
215	ZMPu	19690201	female		

patient initiation visit treatment review visit(s) assessment

patient initials  date of birth dd mm yyyy 15 age 

sex at birth CEM ID no. patient file no.

 Patient details

 save report  save and finalize  save report off-line

- Save report
 - The report is saved to the database
- Save and finalize
 - The report has been assessed and I “finished”
- Save report off-line
 - The report is only saved locally on the client

Patient information

Monitored medicine

Other medicine

Other medicine

Other medicine

Treatment init. visit

Past medical
conditions

Follow up visit

Follow up visit


Follow up visit

CEM report


Assessment

Patient details

patient initiation visit treatment review visit(s) assessment

patient initials 


date of birth dd mm yyyy

age 

sex at birth

CEM ID no.

patient file no.

 Patient details

first name

last name

cell phone

address

town/village

post code

contact person with contact details

If clicking patient details some additional patient fields will "pop up"



Visits

- There are two types of visits
 - Treatment initiation visit – *only one*
 - Treatment review visit – more than one can be added
- The visits are ordered in separate tabs
 - Treatment initiation visit tab and treatment review visit tab

patient initiation visit treatment review visit(s) assessment

date of interview: 15 05 2011 15
 interview site: visit at health centre
 clinician/team: [input field] add clinician/focal person
 body weight at visit (kg): [input field]
 body height at visit (cm): [input field]
 focal person: [input field]

severity of monitored disease: [input field]

medicine being prescribed: [input field]

is the patient pregnant: yes [dropdown] gestation period: [input field]
 is the patient breastfeeding a child: [input field]

Current and past medical conditions

name	start date	end date	continuing
Tuberculosis	01 05 2011 15	dd mm yyyy 15	<input type="checkbox"/>

+ Add medical condition

Events recorded in the comparator period

event	start date	end date
Headache		

eventsuggestion start date end date open
 Headache dd mm yyyy 15 dd mm yyyy 15 add details

+ add event

Laboratory tests results

test name	date	result
HIV antibody	15 05 2011 15	[input field]

+ add test

date of next visit: dd mm yyyy 15
 date of completion of questionnaire: dd mm yyyy 15
 prescriptions at this visit: [input field]

We are in the initiation visit tab

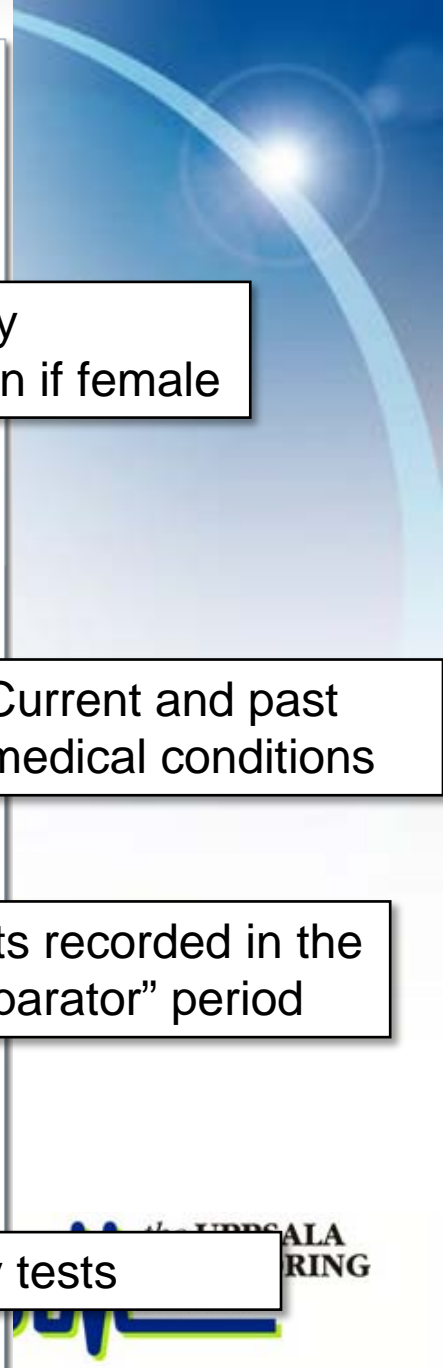
Pregnancy information if female

Current and past medical conditions

Events recorded in the "comparator" period

Add a new event

Laboratory tests



patient initiation visit treatment review visit(s) assessment

date of interview 02 06 2011 15 interview site visit at health centre clinician/team [] add clinician/focal person

body weight at visit (kg) body height at visit (cm) focal person []

visitdate 02.06.2011

add follow up visit

Reporters may differ from one visit to the other

Each visit is listed in a table

Patient weight and height may vary from one visit to another

List of events for this visit

Tick all medicines (from medicine list) taken during treatment

Go to the medicine list

problems or rechallenge results since last seen

end date	open
20 06 2011 15	<input type="checkbox"/>

Back pain 20 06 2011 15 dd mm yyyy 15 add details

outcome severity seriousness rechallenge

U = unknown moderate N - not serious

add event

Abnormal laboratory tests results after starting treatment

test name	date	result
-----------	------	--------

add test

Medicines taken at any time during treatment with the monitored medicine(s)

Abacavir 01.05.2011 open medicine list

Aspirin

Mangeol

Go to medicine list to add or discontinue a new medicine.

date of next visit dd mm yyyy 15

date of completion of questionnaire dd mm yyyy 15

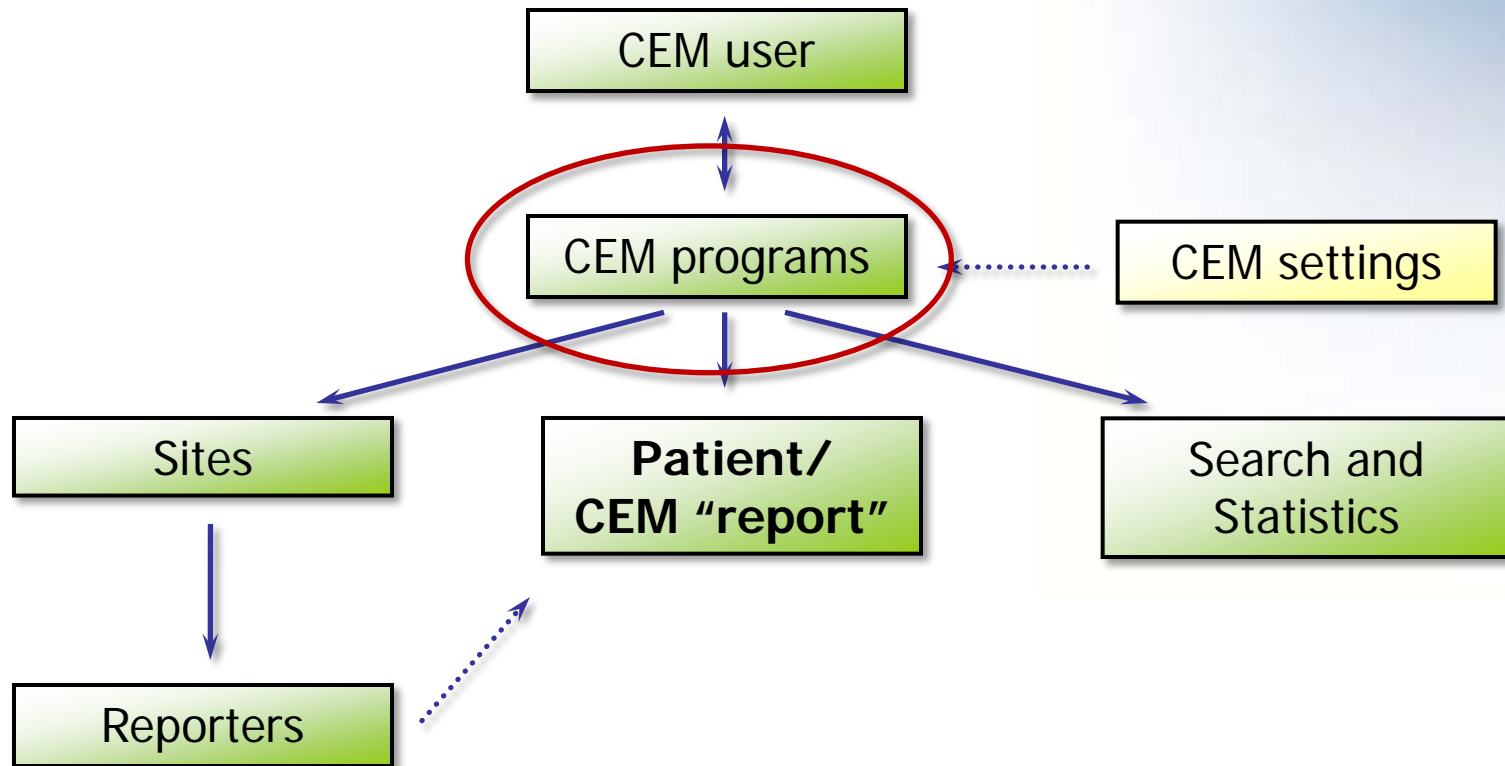
prescriptions at this visit []



So how does CemFlow know what drug to monitor, length of control period etc...?



CemFlow structure



CEM programme

- A CEM programme is the main “entity” of the CemFlow tool.
 - CemFlow supports many CEM programmes in parallel
 - All “reports/patients” and reporters belong to a specific programme
 - Search and Statistics are made on patient reports for a specific programme
 - However, reports from other programmes may in the future be used as comparator/baseline data



CEM programme settings

- A CEM programme has:
 - Organization (“owner” and contact person)
 - Description
 - *Documents (like SOPs, Questionnaires and manuals)*
 - Settings
 - Shown on next page



Comparator period

program name: CEM Malaria for WHO

description: A malaria test and demo program for not country dependent.

responsible organization: WHO

responsible person: Magnus Wallberg

comparator period (days): 7

medical status lexicon: diseasestatus_severity_lx.xml

therapy indication:

program drugs: Artemether, Lumefantrine, Artemether w/lumef

program concomitant condition(s): Tuberculosis

program laboratory test(s):

Name	Low range	High range	Unit
Malaria antibody positive			
Malaria antibody test			
Microscopy			

Buttons: Get default test, save

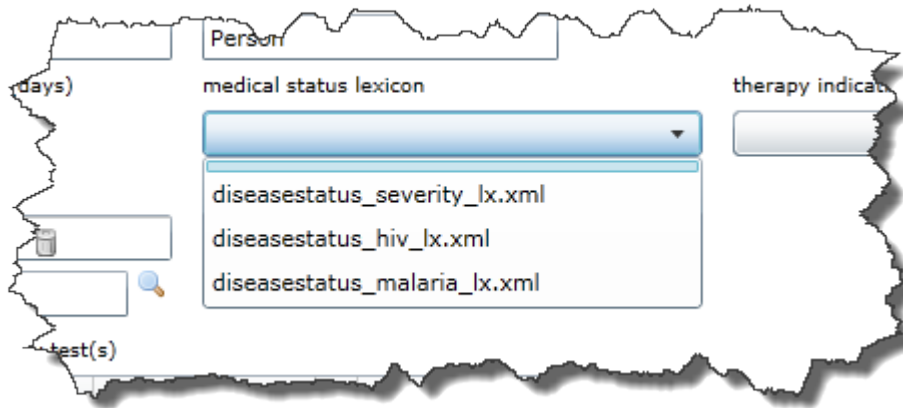
Medical status lexicon

Therapy indication

Monitored drugs

Important co-morbid conditions

Standard tests



- HIV

- HIV WHO clinical stage I
- HIV WHO clinical stage II
- HIV WHO clinical stage III
- HIV WHO clinical stage IV

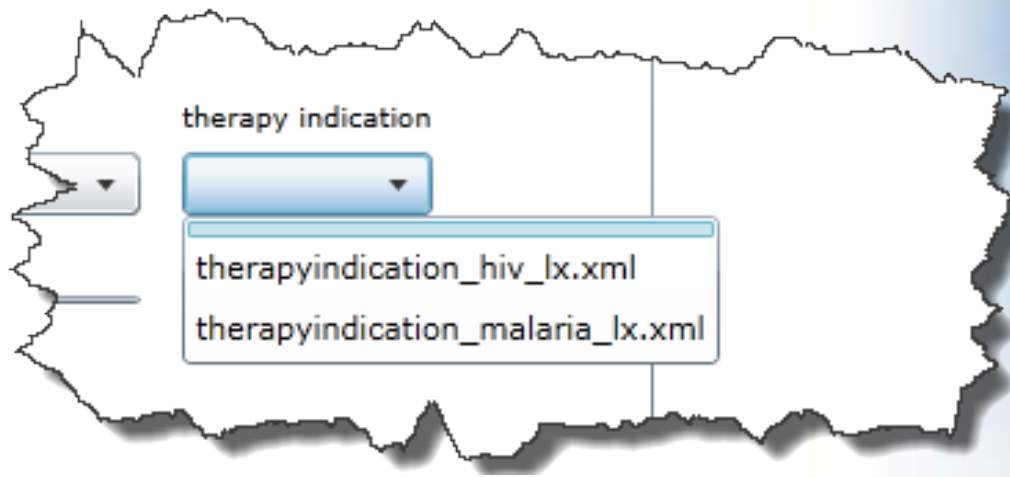
- Malaria

- Uncomplicated
- Severe

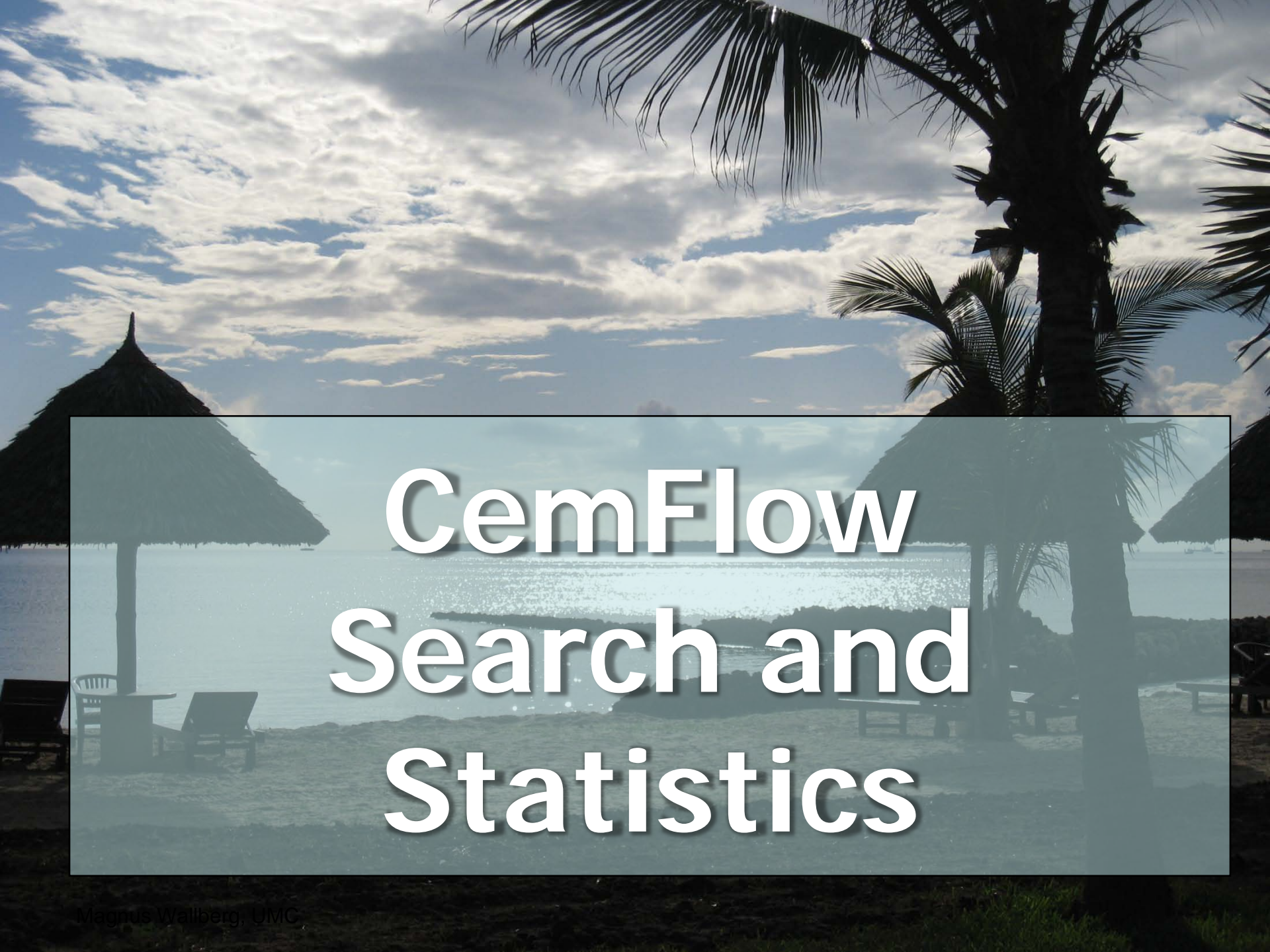
- Severity

- Mild
- Moderate
- Severe



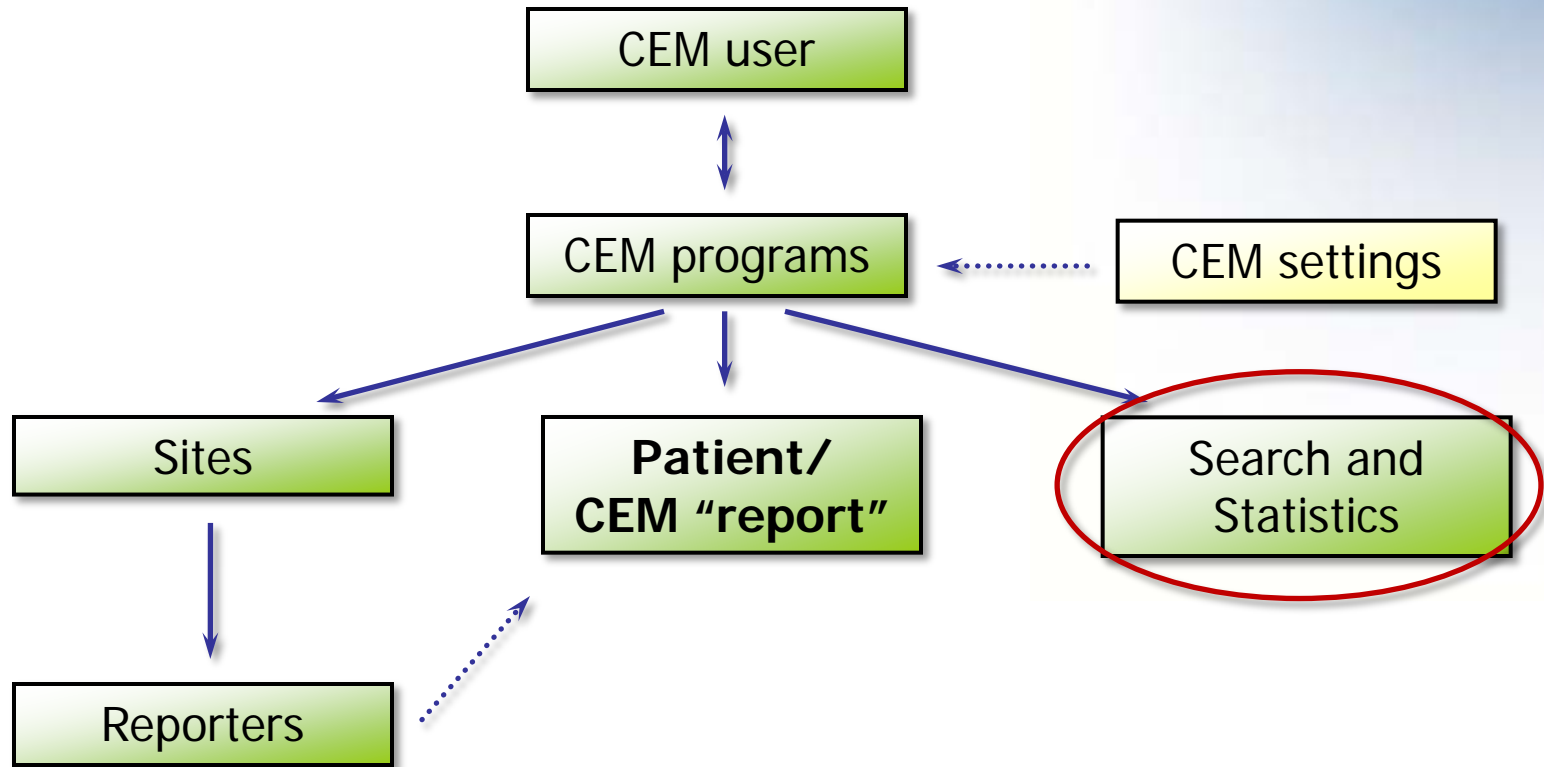


- HIV
 - Treatment of chronic HIV infection
 - Prevention of Mother to Child Transmission
 - Both
- Malaria
 - Presumptive
 - Confirmed



CemFlow Search and Statistics

CemFlow structure



Search and Statistics

- Analysis of the cohort for a selected CEM Programme can be done in the Search and Statistics section
- There are two types of statistics available
 - Administrative statistic
 - Event statistics
- There are also event listings available that can be exported on Excel format for off-line analysis



Welcome to CemFlow

Available CEM programs

Please choose a Cohort Event Monitoring program from the list below in order to get started.

New program 3

CEM ARV for WHO

Demonstration Accra Nov 2011

CEM Study on AMFm Antimalarials (Ghana)

TANCEM - DHA/PPQ

CEM Malaria for WHO

CEM PILOT for Malaria (Nigeria)

Gendy Playground

Demonstration Kiev November 2011

When logging in the menu is "empty"

Begin by selecting a CEM program

main patient data entry search and statistics reporter programs and users terminology manager logout


statistics administrative info


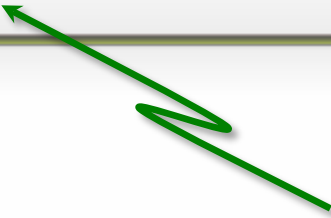
Welcome to CemFlow

Available CEM programs

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- New program 3
- CEM ARV for WHO
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- TANCEM - DHA/PPQ
- CEM Malaria for WHO
- CEM PILOT for Malaria (Nigeria)
- Gendy Playground
- Demonstration Kiev November 2011

Copyright, Uppsala Monitoring Centre  CEM ARV for WHO CemFlow - 3.0.3



Now the Search and Statistics option is available

The active program is displayed in the footer

Administrative statistics

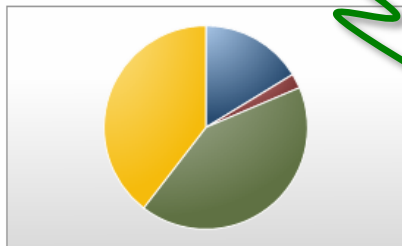
- A sub section of the Search and Statistics tool that provides administrative statistics like:
 - Reporting per clinic and reporter
 - Number of reports in the database
 - Number of reports per drug
 - General distribution of concurrent conditions
 - ...



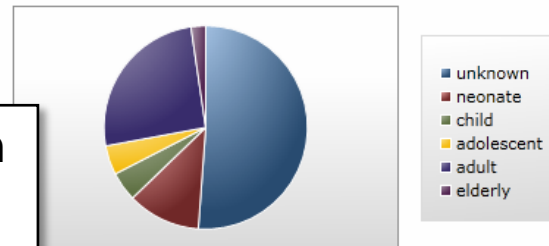
search

generate excel

Gender distribution



Age group distribution

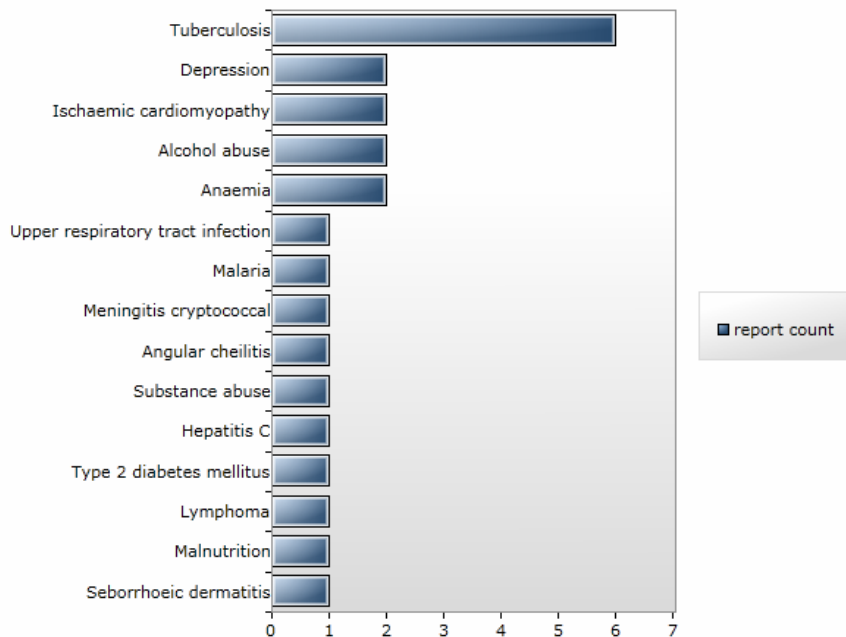


The statistics can be exported on Excel format

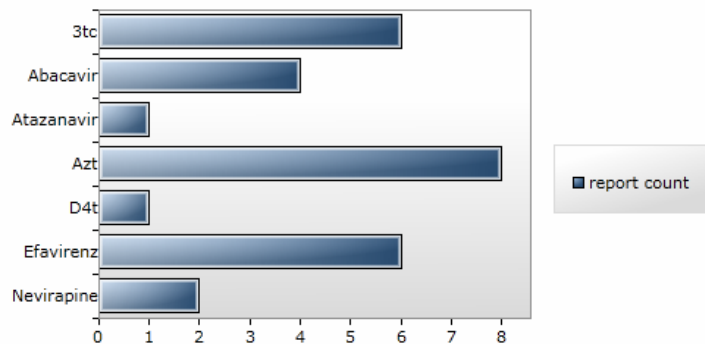
Site distribution



Frequency of concurrent conditions



Number of drugs



Search and Statistics



- The Search and Statistics tool provides standard analysis tools and export functionality
- Predefined profiles with different filters and stratifications are available
- Will be further developed when more data is available and the needs get identified
 - Especially the longitudinal data analysis needs to be developed
 - Research is ongoing at the UMC and will be done also on CEM data during 2012



Profiles

- The different output types are available as tabs
 - Patient/event list
 - A simple patient list with all event listed
 - List of events
 - Stratifications
 - An event list stratified by different strata
 - Groupings on all available CEM terminology levels
 - Summary by Clinical Category
 - Event profile
 - ... others to come



Patient/ event list

List of patients | List of events | Stratifications | Summary by CC | Event statistics

visittypfilter: treatment review visit ▾

search

generate excel

CEM ID	Sex	Age group	Events	
OPQ-234	female	adult	Referred gynaecological pain	
DR0152	male	neonate	Nausea	2
				8
				2
ABCDE	male	adu		
abc	male	uni		
123456	male	unknown		
123450	female	unknown	Nausea	
	female	adolesce		
	male	neonate		
	female	adolesce		368
				367
	male	neonate	Nausea	5
			Gastroenteritis	51
	female	adolescent	Weight loss	
	male	child	Weight loss	
	male	neonate	Weight loss	51

Sorting can be done on CEM ID, sex and age group

The CEM ID is important to be able to find the patient

The "red flag" indicates that the event is written in free text

List of events

List of patients | List of events | Stratifications | Summary by CC | Event statistics

visittypfilter

treatment review visit ▾

search

generate excel

Get the entire list as an Excel file

Possible to sort on all columns

CC	AFC	CSG	PET	Relationship	Time to onset (days)	Sex	AgeGroup	CEM ID
Alimentary	Functional	An				male	adult	ABCDE
Alimentary	Functional	Na		Possible	5	male	neonate	
Alimentary	Functional	Na			2	male	neonate	DR0152
Alimentary	Functional	Na				female	unknown	123450
Alimentary	Gastroenteritis	Gastroenteritis	Gastroenteritis	Unlike			neonate	
Endocrine/metabolic	Nutritional change	Malnutrition	Weight loss	Possil			adolescent	
Endocrine/metabolic	Nutritional change	Malnutrition	Weight loss				child	
Endocrine/metabolic	Nutritional change	Malnutrition	Weight loss	Possible	51	male	neonate	
Endocrine/metabolic	Lipid metabolism	Cholesterol abnormal	Cholesterol increased			male	neonate	
Ear Nose & Throat	Oropharynx	Throat infection	Sore throat		515	female	adolescent	
Haematological	Anaemia not specified	Anaemia	Anaemia NOS			male	unknown	abc
Haematological	Anaemia not specified	Anaemia	Anaemia NOS	Possible	41	male	neonate	
Infection	Fungal infection	Candida	Candidiasis			male	child	
Infection	Parasitic infection	Protozoal	Malaria		8	male	neonate	DR0152
Mental Health	Psychosis	Psychosis	Psychosis			male	neonate	
Neurological	Headache	Headache	Headache	Possible	10	male	neonate	
Neurological	Headache	Headache	Headache		2	male	neonate	DR0152
Reproductive organs	Pregnancy	Normal pregnancy	Pregnancy	No relationship		female	adolescent	
Respiratory	Respiratory infection	Acute upper respiratory infection	Pharyngitis			male	child	
Skin	Dermatitis	Rash generalised	Rash maculopapular			male	unknown	123456
Skin	Dermatitis	Rash generalised	Stevens Johnson Syndrome		46	male	child	

Excel output

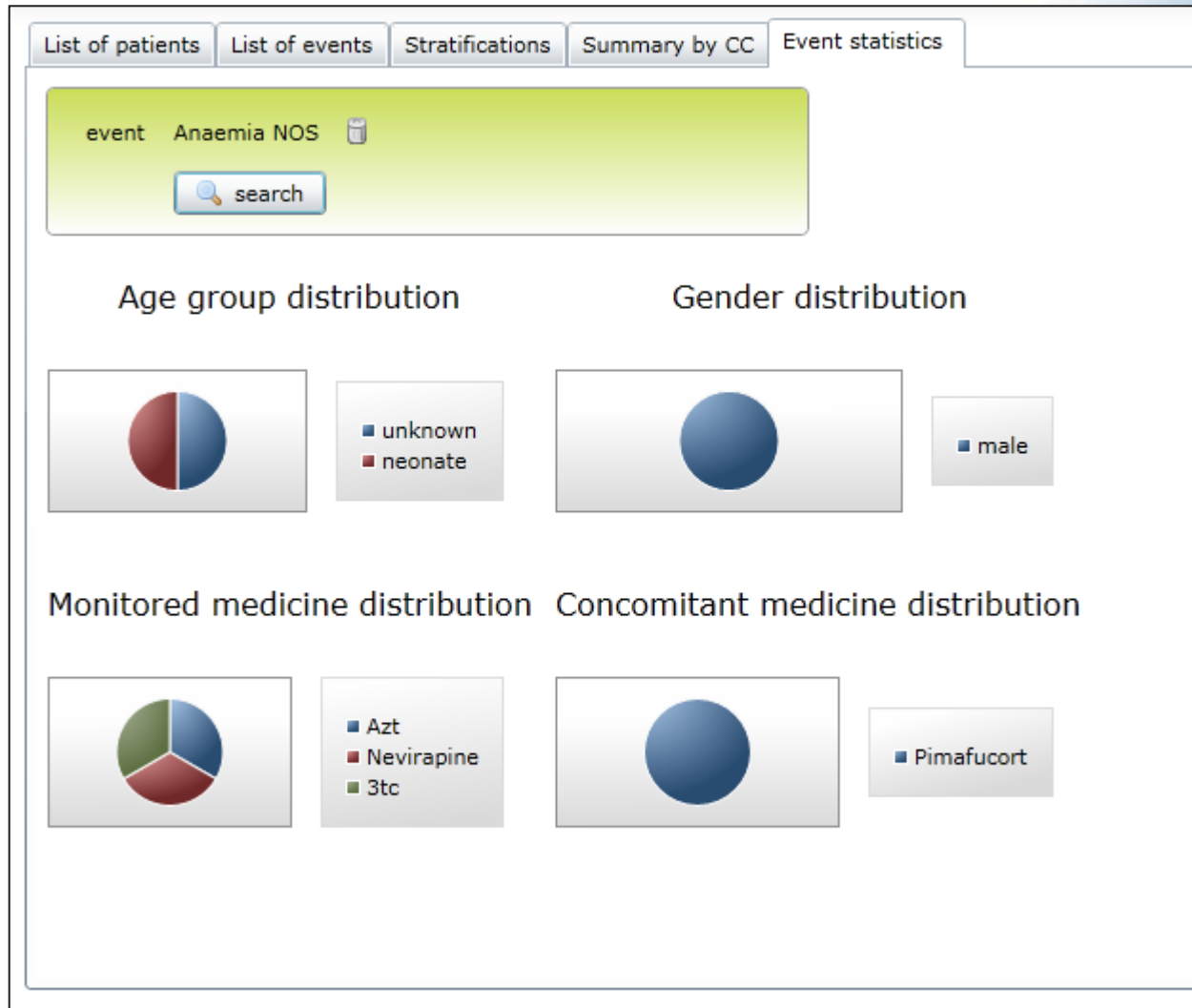
	A	B	C	D	E	F	G	H	I
1	CC	AFC	CSG	PET	Relationship	Time to onset	Sex	Age group	CEM ID
2									
3	Accidents	Violence	Violence	Plane crash			male	unknown	123456
4	Accidents	Violence	Violence	Plane crash			male	child	000-111
5	Alimentary	Functional	Anorexia	Anorexia			male	adult	ABCDE
6	Alimentary	Functional	Nausea	Nausea	Possible	5	male	neonate	
7	Alimentary	Functional	Nausea	Nausea		2	male	neonate	DR0152
8	Alimentary	Gastroenteritis	Gastroenteritis	Gastroenteritis	Unlikely	51	male	neonate	
9	Alimentary	Diarrhoea	Diarrhoea	Diarrhoea			female	adult	A00001
10	Alimentary	Diarrhoea	Diarrhoea	Diarrhoea			male	adult	ABCDE
11	Alimentary	Diarrhoea	Diarrhoea	Diarrhoea			male	neonate	DR0152
12	Alimentary	Diarrhoea	Diarrhoea	Diarrhoea			male	elderly	A00003
13	Autonomic	Temperature reg	Fever	Fever			male	elderly	A00003
14	Endocrine/metabolic	Nutritional chan	Malnutrition	Weight loss	Possible	51	male	neonate	
15	Endocrine/metabolic	Nutritional chan	Malnutrition	Weight loss	Possible		female	adolescent	
16	Endocrine/metabolic	Nutritional chan	Malnutrition	Weight loss			male	child	
17	Endocrine/metabolic	Uric acid metabol	Gout	Gout			male	neonate	
18	Endocrine/metabolic	Lipid metabolism	Cholesterol abno	Cholesterol increased			male	neonate	
19	Ear Nose & Throat	Oropharynx	Throat infection	Sore throat		515	female	adolescent	
20	Ear Nose & Throat	Oropharynx	Throat infection	Tonsillitis			male	neonate	
21	Ear Nose & Throat	Oropharynx	Throat infection	Tonsillitis			male	child	
22	Haematological	Anaemia not sp	Anaemia	Anaemia NOS			male	unknown	abc
23	Haematological	Anaemia not sp	Anaemia	Anaemia NOS			male	unknown	abc
24	Haematological	Anaemia not sp	Anaemia	Anaemia NOS	Possible	41	male	neonate	
25	Haematological	Anaemia not sp	Anaemia	Anaemia NOS			female	adult	A00001
26	Infection	Fungal infection	Candida	Candidiasis			male	child	
27	Infection	Parasitic infecti	Protozoal	Malaria		8	male	neonate	DR0152
28	Mental Health	Psychosis	Psychosis	Psychosis			male	neonate	
29	Neoplasms	Abdominal/alim	Alimentary	Carcinoma stomach			male	unknown	123456
30	Neurological	Headache	Headache	Headache	Possible	10	male	neonate	
31	Neurological	Headache	Headache	Headache		2	male	neonate	DR0152
32	Reproductive organs	Pregnancy	Normal pregnanc	Pregnancy	No relationship		female	adolescent	
33	Respiratory	Respiratory inf	Acute upper resp	Upper respiratory tract infection			male	adult	ABCDE

Event statistics

- Contains:
 - Distributions – monitored medicine, gender, age group, concomitant diseases...
- Will also contain:
 - Counts
 - List of individual reports
 - List of terms in hierarch beneath the “active” term
 - With drill down possibilities
 - Longitudinal profiles
 - ...



Event statistics cont...



Excel output



- By clicking “generate Excel” an Excel file is created that can be downloaded locally
- Excel export available for most profiles
 - Also available when it is not possible to display the result because of too much data
- The Excel file is generated on XML format
- Client requirements for Excel
 - Microsoft Office 2003 (*or later*)

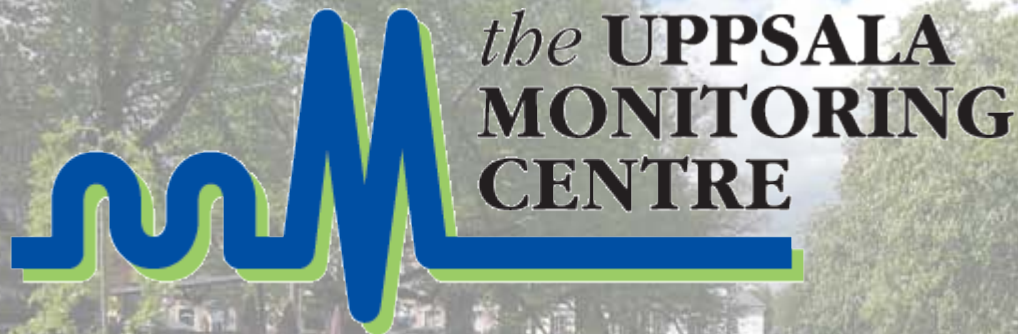
Finally...

CEM is **not a replacement** for other surveillance methods...

It is designed to add **more** knowledge about drugs and vaccines already on the market!

Reporting





the **UPPSALA
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