Epidemiological studies

Module 2.2

World Health Organization European Region

UNECE

Steps in outbreak management

1. Detect and confirm the outbreak and agent
2. Rapid Response Team (RRT)
3. Define cases
4. Identify cases and obtain information
5. **Descriptive epidemiological investigation (time, place, person)**
6. Additional studies (environmental, risk assessments, laboratory)
7. Interview cases and generate hypotheses
8. **Evaluate the hypotheses**
9. Inform risk managers and implement control measures
10. Communicate findings, make recommendations and evaluate the outbreak response

Communication Measures

Epidemiological studies

- Descriptive
- Ecological
- Analytical
  - Cohort studies
  - Case-control studies

Descriptive analysis

They answer the question *"What's going on?"*

Person

- Who?

Place

- Where?

Time

- When?

Descriptive analysis

- Generate hypotheses on the possible source, etiology and modes of transmission
- Identify the population at risk
- Estimate when the initial exposure to the causative pathogen occurred
- Identify opportunities for control

Descriptive analysis

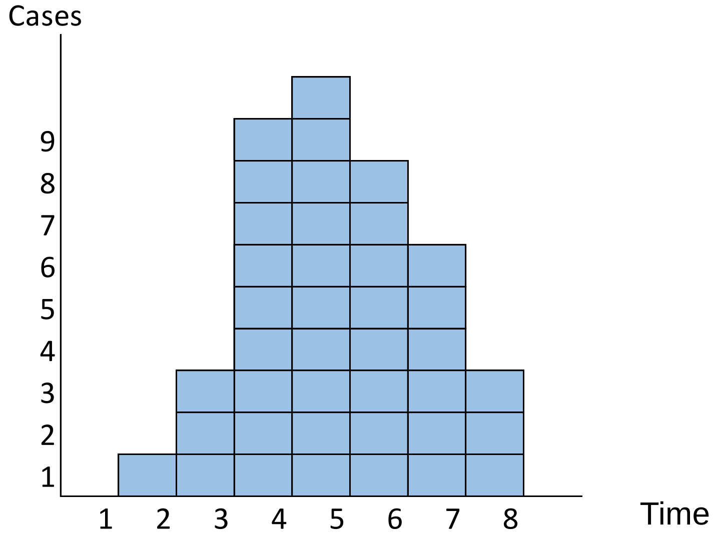
- Results visualized in tables and maps or curves
- Not possible to identify causality or risk factors

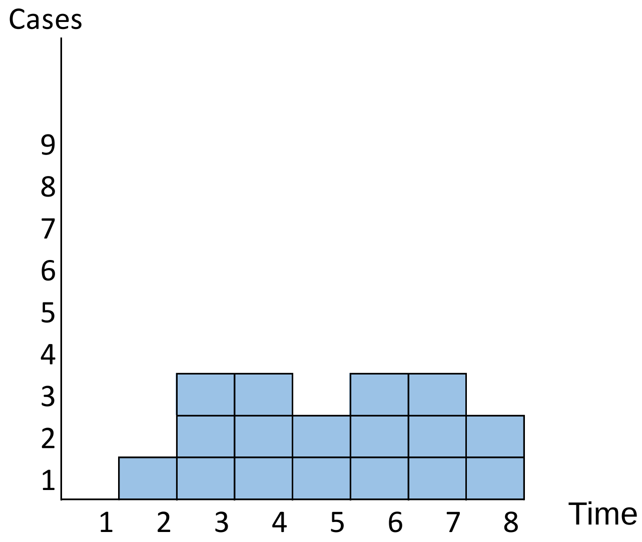
Time- when?

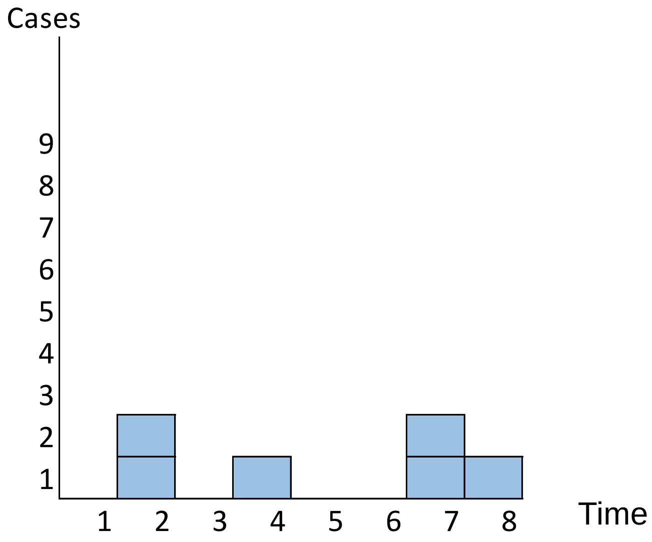
The epidemic curve indicates

1) Type of source: point source, continuous, intermittent

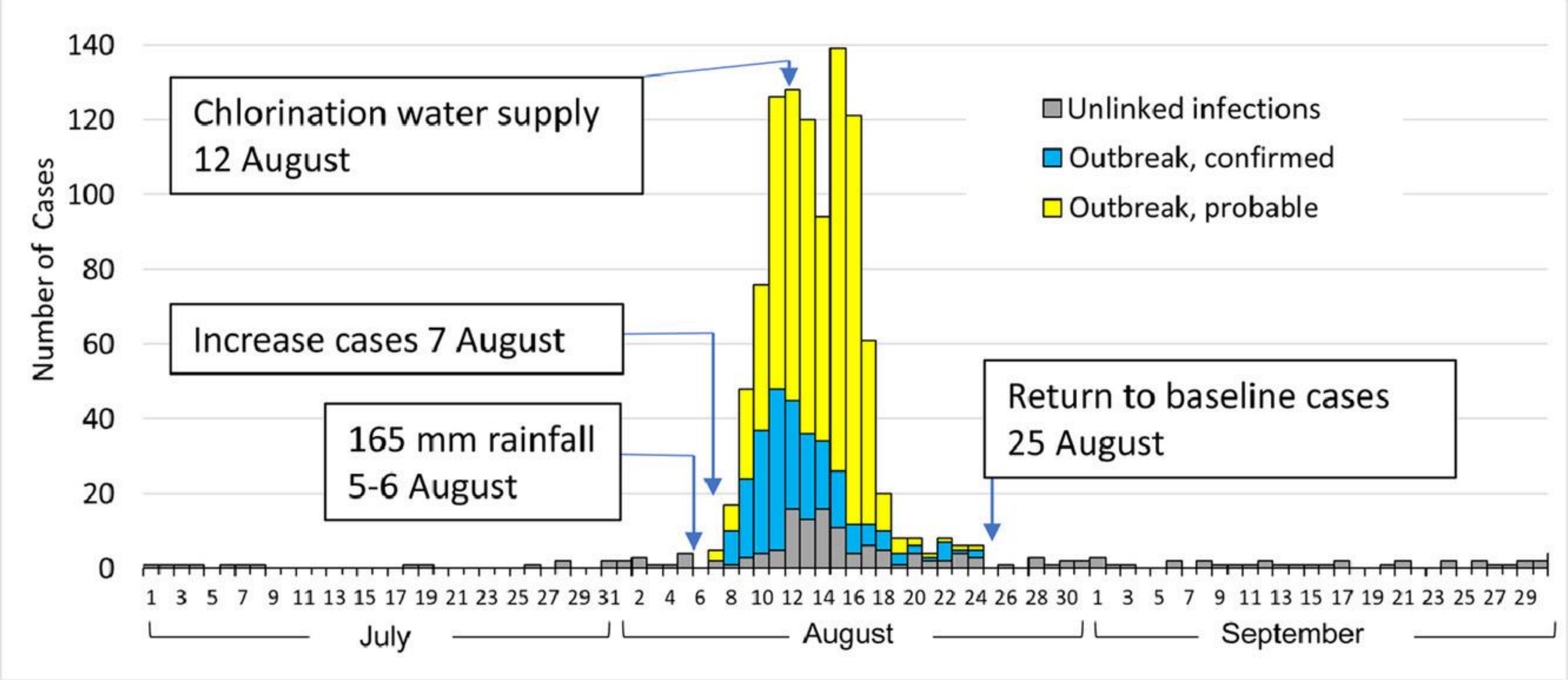
2) Mode of transmission







Time- when?

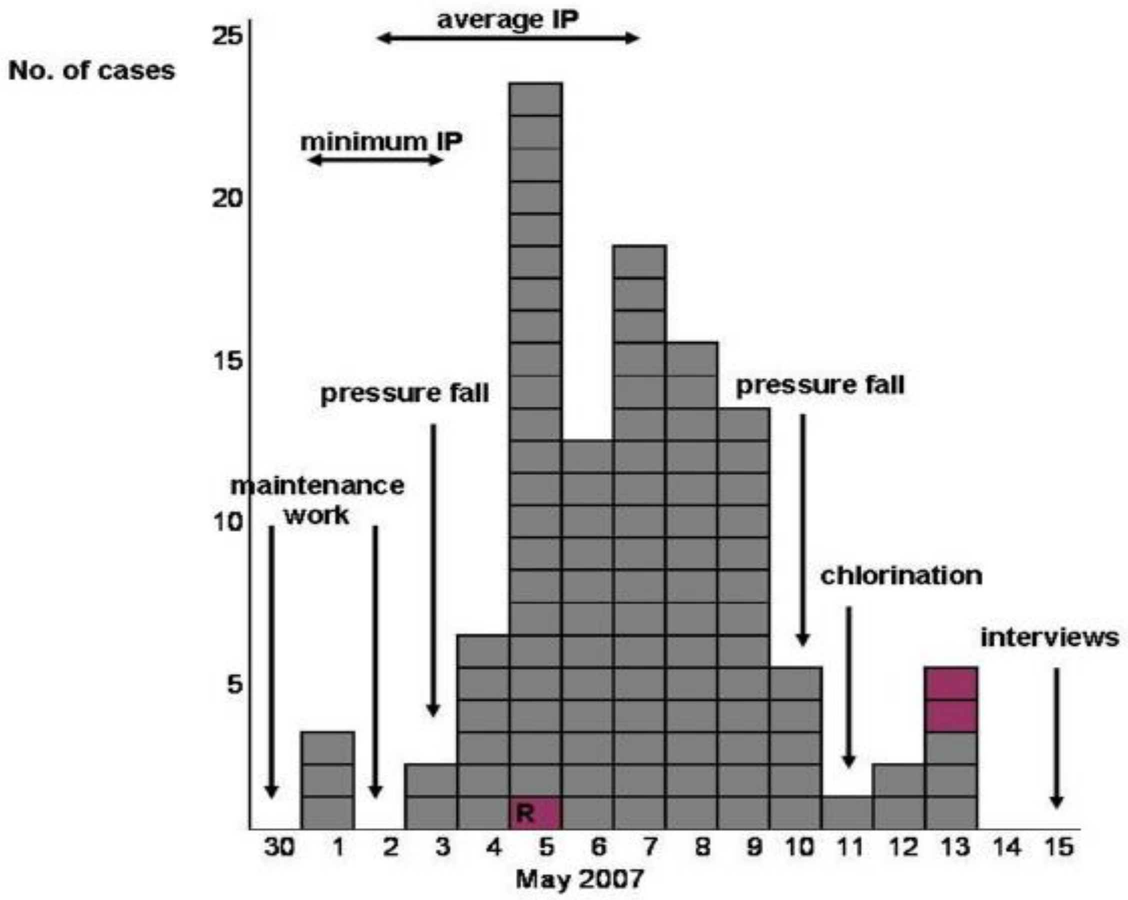


Reported campylobacteriosis in Hawke´s Bay from July to September 2016 graphed according to onset of symptoms.

Confirmed, probable and unlinked reported campylobacteriosis cases

Gilpin et al. (2020): A large scale waterborne Campylobacteriosis outbreak, Havelock North, New Zealand. Journal of Infection, https://doi.org/10.1016/j.jinf.2020.06.065

Time- when?



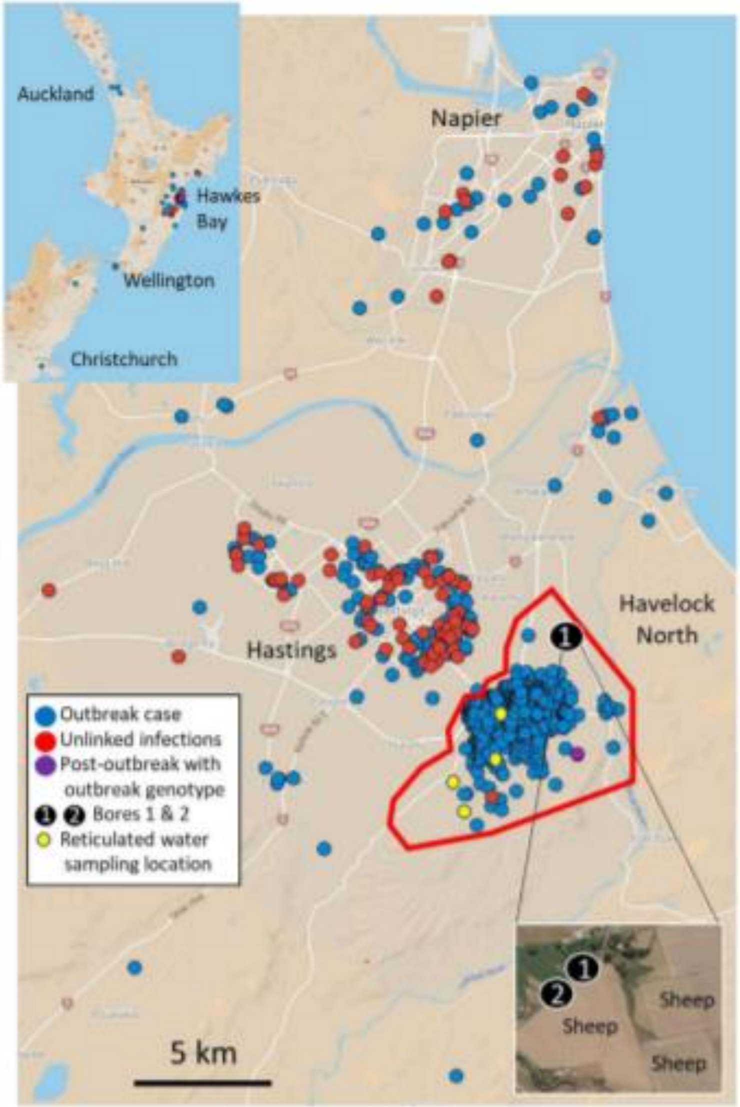
Cases of gastroenteritis in a sample of Røros (Grey) and Holtalen (Plum) household members by date of illness onset (n = 105), from April 30 to May 14, 2007 and the timeline of events, which may be relevant to the water contamination.

Jakopanec et al. (2008): A large waterborne outbreak of campylobacteriosis in Norway: The need to focus on distribution system safety. BMC Infectious Disease, https://doi.org/10.1186/1471-2334-8-128

Place- where?

- Cases mapped to assess the geographical extent of the outbreak
- Visualize and explore the spatial distribution of cases
- A cluster of cases might suggest exposure to a particular source
- Attack rates by exposure to particular water sources and by place
- Visualize and explore the spatial distribution of cases

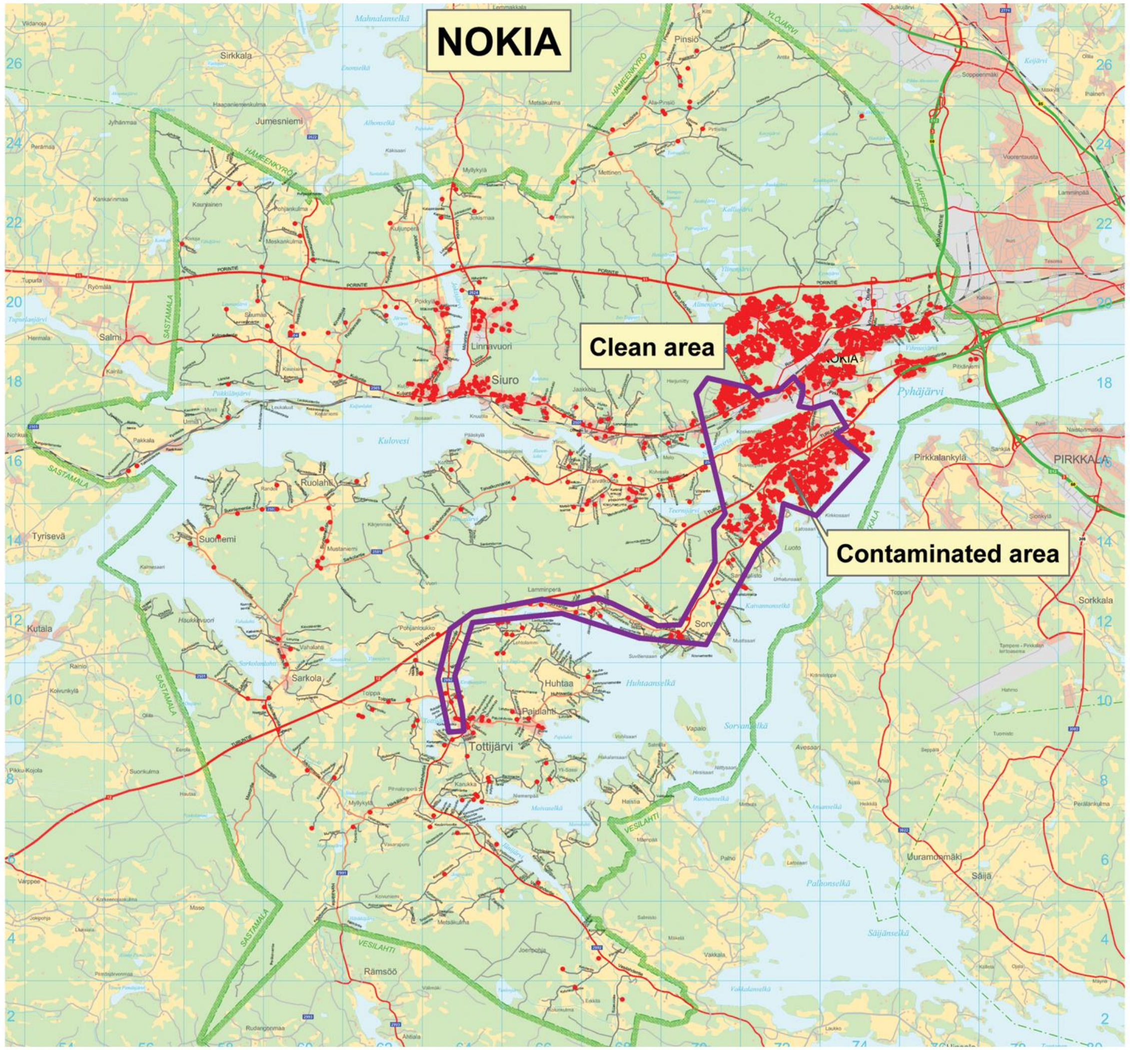
Place- where?



Geographic distribution of outbreak cases, and unlinked infections with onset of illness of 7–24 August 2016. Also shown is the Havelock North contaminated reticulation area (red box), and locations of the reticulated network sampling points, bores and sheep paddocks

Gilpin et al. (2020): A large scale waterborne Campylobacteriosis outbreak, Havelock North, New Zealand. Journal of Infection, https://doi.org/10.1016/j.jinf.2020.06.065

Place- where?



Halonen et al. (2012): Waterborne Outbreak of Gastroenteritis: Effects on Sick Leaves and Cost of Lost Workdays. PLOS ONE, https://doi.org/10.1371/journal.pone.0033307

Person- who?

- Age
- Sex
- Number of cases
- Attack rate
- Symptoms
- Hospital admission
- Deaths
- Case fatality rate
- Other?: Ocuppation....

Person-who?

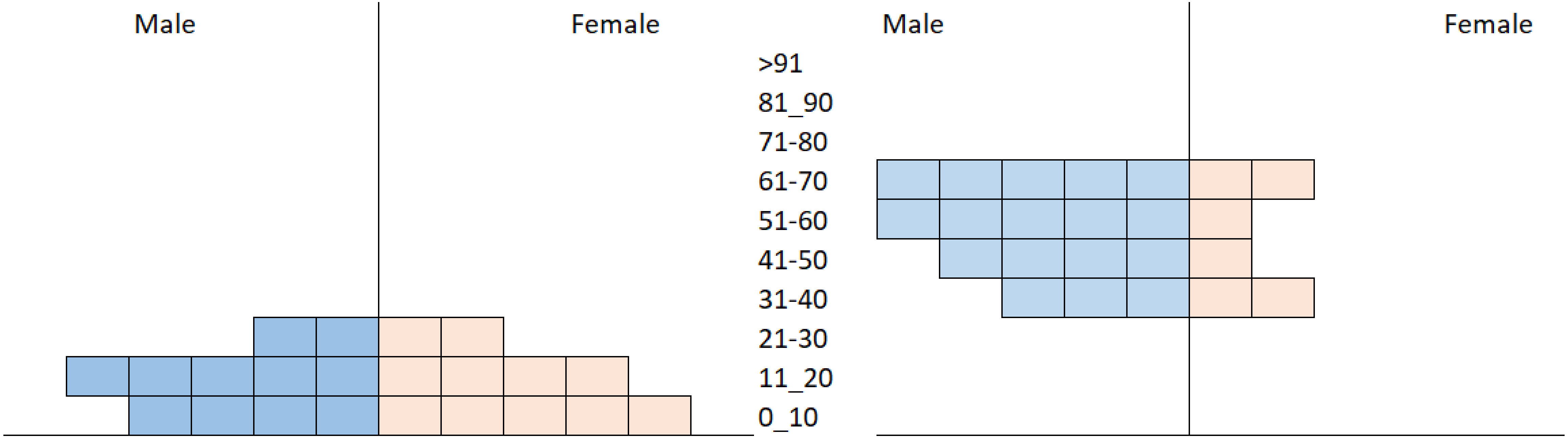
Demographic	Cases	Rates per 100,000 with 95% confidence intervals	*p*-value by group
Sex			0·795
Female	497	595·2 (544·1, 649·7)	
Male	456	584·7 (532·4, 640·8)	
Age group			<0·001
<5	61	553·3 (423·5, 710·2)	
5–19	184	532·4 (458·4, 614·9)	
20–59	326	425·5 (380·6, 474·1)	
≥60	382	972·4 (877·7, 1074·4)	
Ethnicity			<0·001
Māori	100	296·4 (241·2, 360·3)	
Pacific	17	284·0 (165·6, 454·4)	
Asian	29	580·2 (388·9, 832·3)	
European	802	716·8 (668·2, 768·0)*	
Other	5	146·1 (47·5, 340·6)	
Age group amongst hospitalized			<0·001
<5	1	9·1 (0·2, 50·5)	
5–19	1	2·9 (0·1, 16·1)	
20–59	7	9·1 (3·7, 18·8)	
≥ 60	31	78·9 (53·6, 112·0)*	
Serious outcomes			
Deceased	4		
Guillain-Barré syndrome	3		

*Rate in European ethnicity and hospitalized ≥60 years is significantly higher than other sub populations.

Demographic characteristics and clinical outcomes of confirmed and probable campylobacteriosis cases.

Gilpin et al. (2020): A large scale waterborne Campylobacteriosis outbreak, Havelock North, New Zealand. Journal of Infection, https://doi.org/10.1016/j.jinf.2020.06.065

Person- who?


Male
Female
>91
81_90
71-80
61-70
51-60
41-50
31-40
21-30
11_20
0_10
Male
Female

Descriptive analysis, in conclusion

The W's of descriptive epidemiology:

- **W**hat → health issue of concern
- **W**ho → person
- **W**here → place
- **W**hen → time

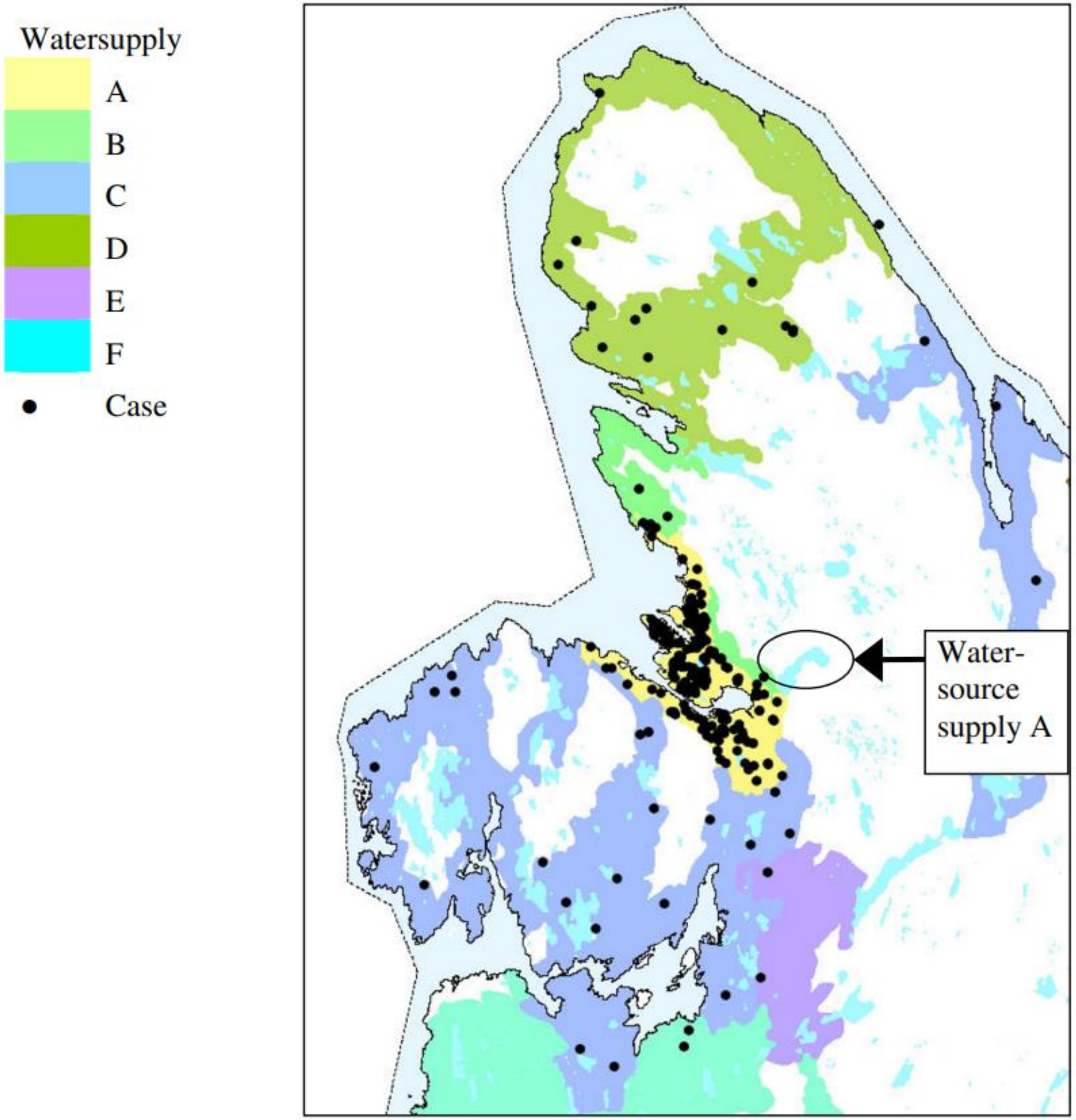
Descriptive analysis, in conclusion

- **Analyse by person:**
  - calculate attack rates by exposure to particular water sources
- **Analyse by place:**
  - calculate attack rates by place
  - map cases distribution to assess the geographical extent of the outbreak
  - Undertake spatial analyses to visualize the spatial distribution of cases in relation to suspect sources.
- **Analyse by time:**
  - if the causative agent is known, use the epidemic curve to estimate the likely time period of exposure
  - Assess if the epidemic curve correlates with events in the water-supply system and implementation of control measures

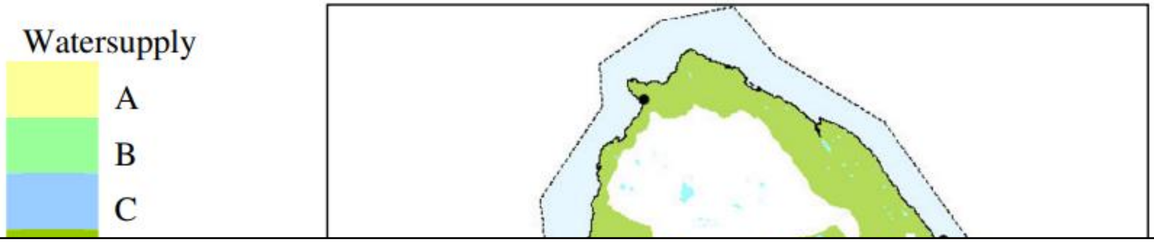
Water supply zones of water supply system WSS-A defined by different reservoirs Zones 6, 7 and 8 were served by Reservoir X.

Estimated incidence rates for gastroenteritis consultations linked to reservoir supply zones

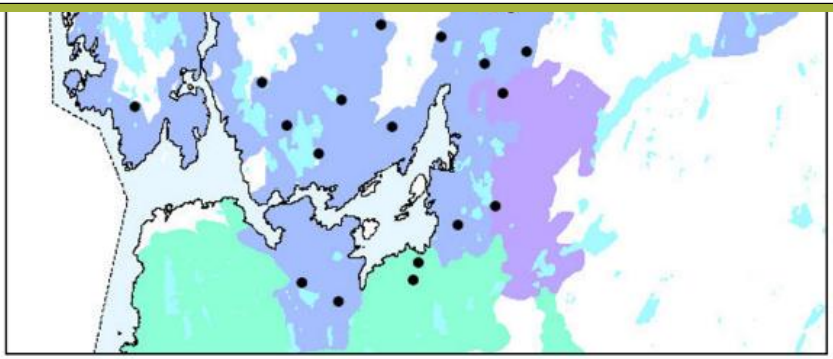
Hyllestad et al. (2020): Large waterborne *Campylobacter* outbreak: use of multiple approaches to investigate contamination of the drinking water supply system, Norway, June 2019. Eurosurveillance, https://doi.org/10.2807/1560-7917.ES.2020.25.35.2000011



Nygård et al. (2006): A large community outbreak of waterborne giardiasis- delayed detection in a non-endemic urban area. BMC Public Health, https://doi.org/10.1186/1471-2458-6-141



Watersupply	Cases	Number of recipents	Attack-rate (per 10,000)		
A	637	42,774	148.9		
B	15	9,685	15.5		
C	89	105,440	8.4		
D	33	34,406	9.6		
E	4	14,266	2.8		
F	13	23,848	5.5		
				Risk ratio	95% confidence interval
B+C+D+E+F	158	194,519	8.1	Ref.	
A	637	42,774	148.9	18.3	15.4 – 21.8



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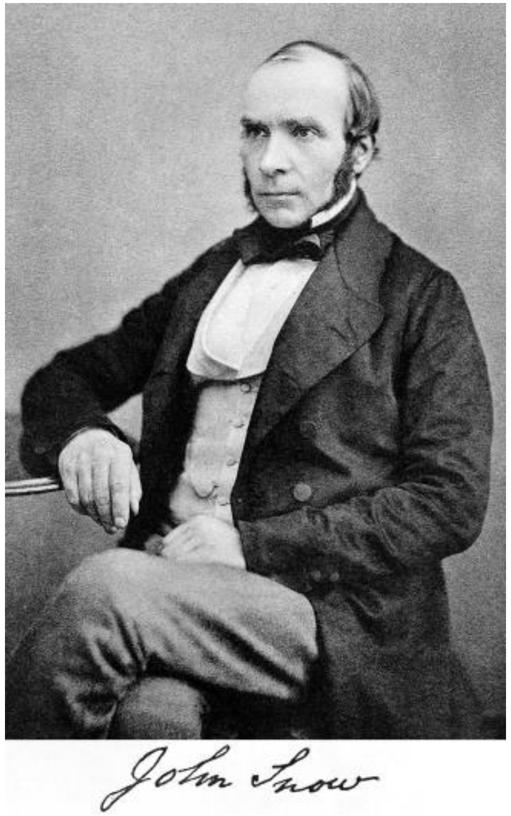
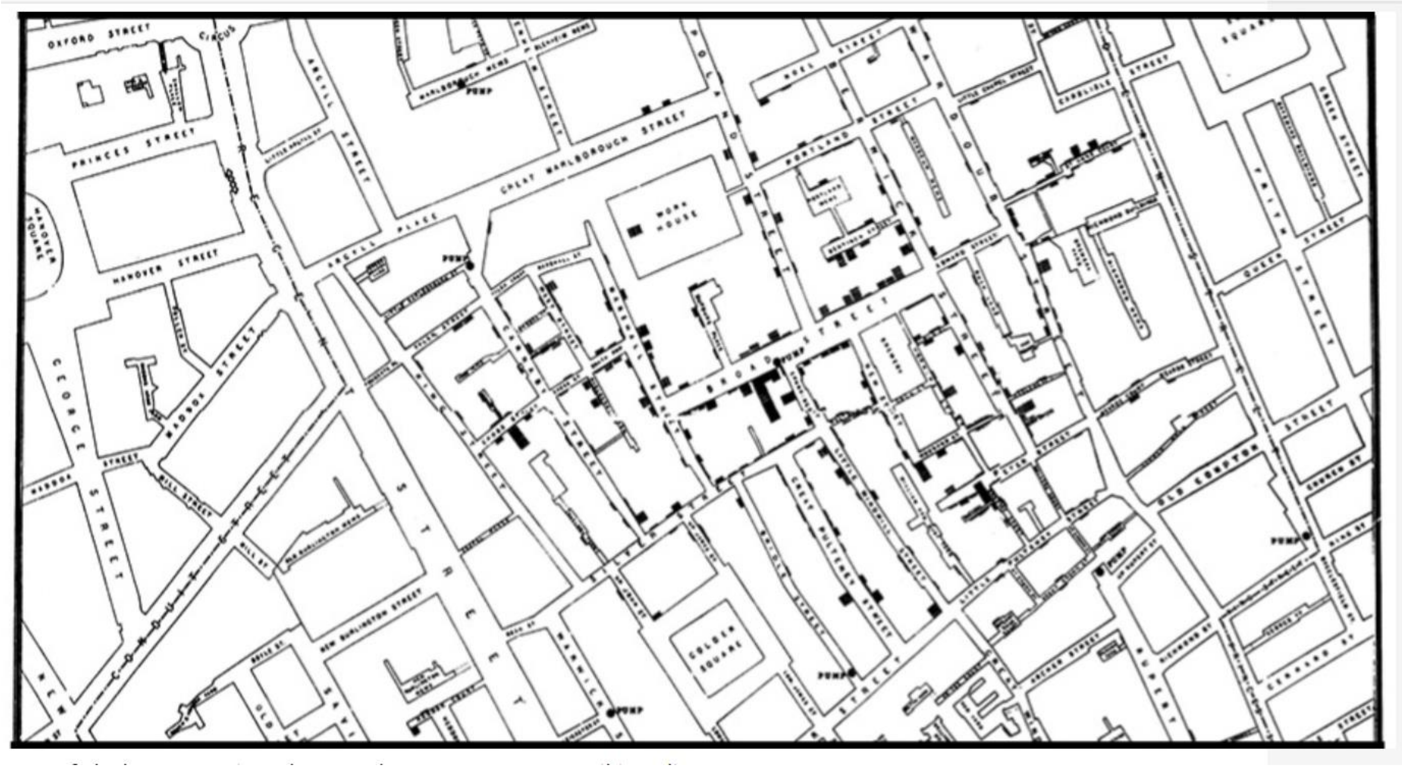
John Snow and Cholera outbreak in London



Source: Field epidemiology manual wiki



Source: CDC

Ecological studies

- Quite useful for outbreaks associated with public water supplies
- They relate to population level, not individual level
- Rates of disease and their association with exposures are compared among defined populations.

Analytical studies

"Are there any differences between what sick and not sick people did?"

- They help to identify exposures associated with disease
- Generate evidence to support the hypothesis under investigation
- Estimate the strength of the association between an exposure and an outcome.
- In outbreak investigations: **retrospective cohort studies, case-control studies**

Analytical studies

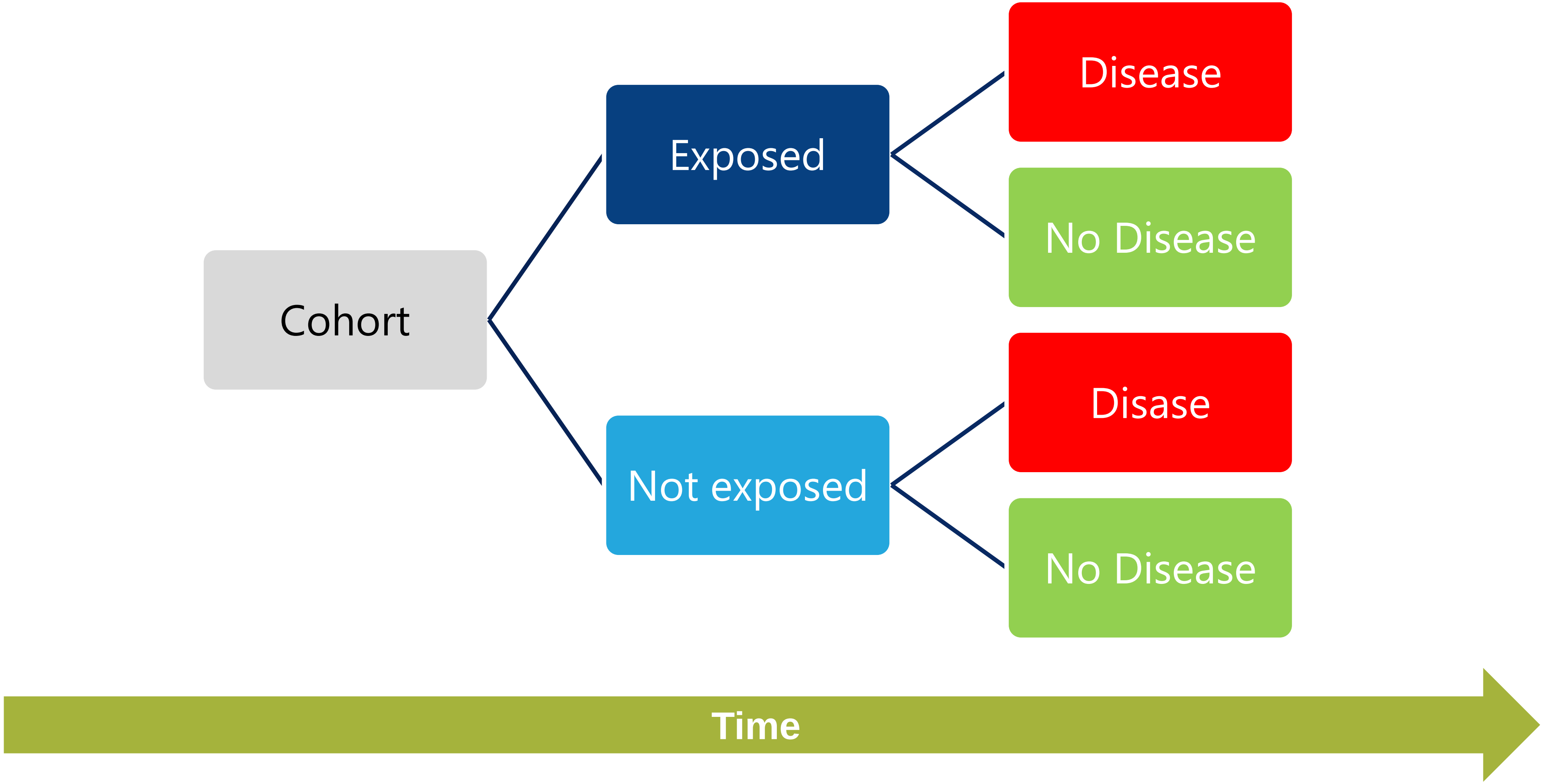
(retrospective) cohort studies

case-control studies

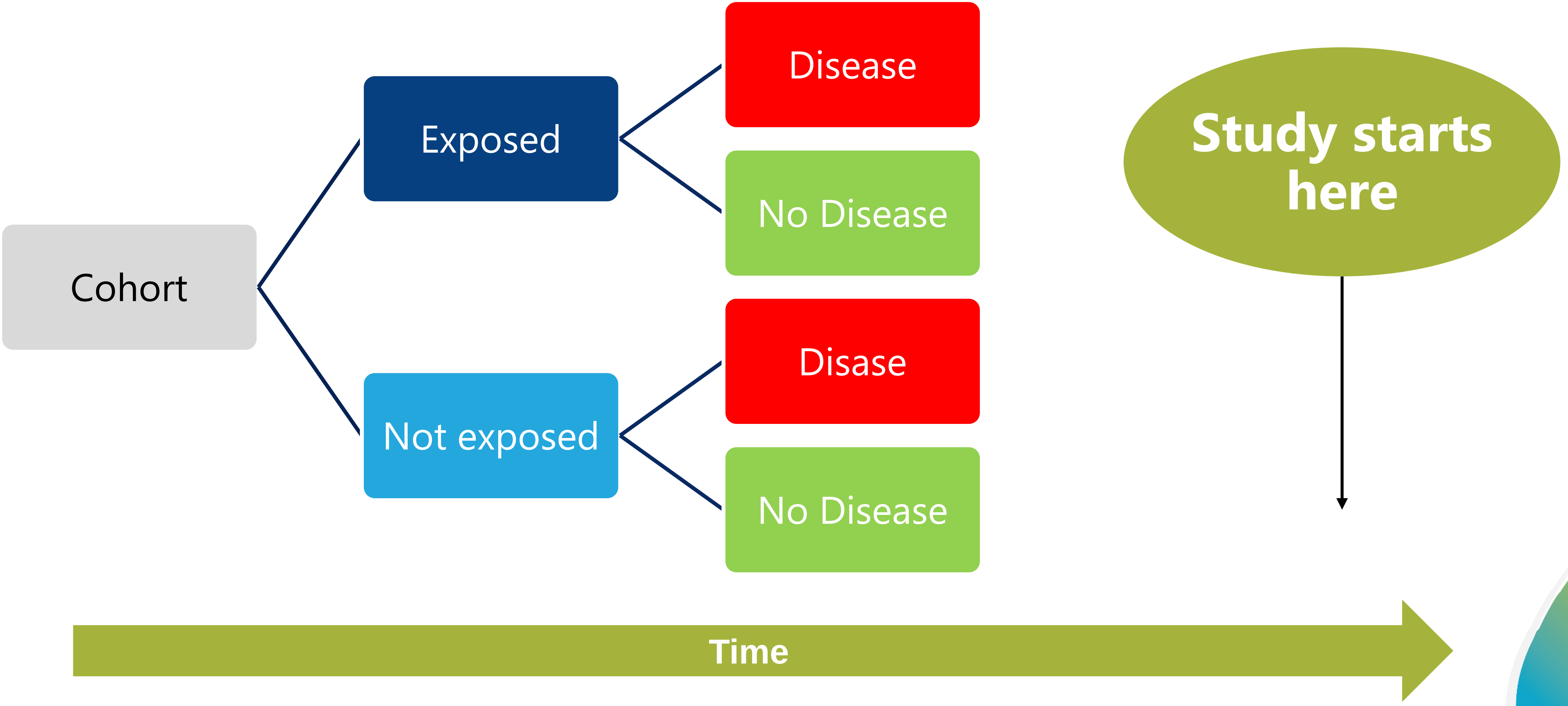
Analytical studies - Cohort studies

- Comparison of risk of disease over a defined time period among those exposed to factor X, versus those not exposed
  - Two cohorts: exposed and not exposed
- If those exposed have a higher rate of disease, this provides evidence that the factor is the cause of the disease.
- This assumes that both groups are the same, except in terms of their exposure to the factor.

Analytical studies- Cohort studies



Analytical studies- Retrospective Cohort studies



Analytical studies- Cohort studies

	Disease	No disease	
Exposed	a	b	a+b
Not Exposed	c	d	c+d
	a+c	b+d	

Attack rate (incidence) in exposed: a/a+b

Attack rate (incidence) in not exposed: c/c+d

→ **Relative Risk (RR):** Incidence in exposed/incidence in not exposed

Relative Risk- Interpretation

- RR = 1; no association
- RR > 1; the exposure is a **risk** factor
- RR < 1; the exposure is a “protective” factor

Cohort study - example

Boccia et al. (2002): Waterborne Outbreak of Norwalk-Like Virus Gastroenteritis at a Tourist Resort, Italy. Emerging Infectious Diseases, https://wwwnc.cdc.gov/eid/article/8/6/01-0371_article

Country example

Cohort study- example

Outbreak context

- July 2000, outbreak of gastroenteritis at a tourist resort in southern Italy.
- Illness in 344 people, 69 staff members
- Norwalk-like virus was found in stool specimens
- The source was likely contaminated drinking water
  - Breakdown in the water system
  - Tap water samples with fecal bacteria

Boccia et al. (2002): Waterborne Outbreak of Norwalk-Like Virus Gastroenteritis at a Tourist Resort, Italy. Emerging Infectious Diseases, https://wwwnc.cdc.gov/eid/article/8/6/01-0371_article

Country example

Cohort study- example

Epidemiological investigation

Case definition: Guest/employee at the resort during July 1–31 and who had diarrhea (≥3 loose stools in 24-hour period) or vomiting (at least 1 episode) or both, in the same period.

Retrospective Cohort study: Because of the high number of cases in staff members, performed to assess risk factors in this group.

- Inclusion criteria: staff members employed from July 1 to 31.
- Questionnaires sent to all 224 staff members in the first week of August.
- A month had elapsed between onset of symptoms and distribution of the questionnaires.

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Country example

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- Inclusion criteria: staff members employed from July 1 to 31.
- Questionnaires sent to all 224 staff members in the first week of August.
- A month had elapsed between onset of symptoms and distribution of the questionnaires.

- 181 questionnaires from 224 staff members were analyzed.
- Attack rate = 38.1% (69/181)

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Cohort study- example

Table 3. Attack rates and relative risks according to usual behaviors and activities of staff members, tourist resort, Italy, July 2000

Exposure	No. (n=69)	No. exposed	Attack rate (%)	Relative risk	95% CI [a]
Shower on the beach	22	14	63.6	1.8	1.2–2.6
Swimming in the pool	45	22	48.9	1.4	0.9–2.0
Drinking tap water	104	47	45.2	1.4	0.9–2.2
Drinks with ice	128	55	43.0	1.8	1.0–3.2
Swimming in the sea	72	31	43.0	1.2	0.8–1.7
Eating at resort restaurant	159	64	40.2	1.5	0.5–3.9
Eating ice cream	140	56	40.0	1.1	0.6–1.9
Eating meat	151	60	39.7	1.2	0.6–2.4
Eating salad	123	48	39.0	1.0	0.6–1.6
Eating fruit	139	54	38.8	1.0	0.6–1.8
Eating pasta	142	55	38.7	1.2	0.6–2.1
Consuming drinks on draught	91	35	38.5	1.0	0.7–1.4
Eating fish	112	40	35.7	0.7	0.5–1.1
Eating seafood	85	28	32.9	0.7	0.5–1.1

[a]CI, confidence interval.

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Analytical studies

(retrospective) cohort studies

case-control studies

Analytical studies - Case-control studies

- Most frequent analytical approach in waterborne outbreaks
- Cases are compared to individuals unaffected by the disease in question to find out whether there is a difference in their exposures
- These unaffected individuals are called "controls"

Analytical studies - Case-control studies

- Who are right controls? That is crucial for success
- Controls must represent the population at risk of disease and must not have the disease under investigation at the time of their recruitment.
- Prevent and address the confounding and selection bias in sampling controls
- Controls represent the background level of exposure in the population.
- If the level of exposure is greater among cases than controls, this provides evidence that the exposure is associated with disease.

Example of control selection

135 cases of *Cryptosporidium hominis*

- **Where?** City XX (population 350.000)
- **When?** Second week September 2020-first week October 2020
- **Who?** 47% Women; mean age 37 years old. Range: 19-91

Example of control selection

135 cases of *Cryptosporid*

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Who are the right controls for a case-control study?

Example of control selection

135 cases of *Cryptosporid*

- **Where?** City XX (po 0)
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- **Who?** 4 ean age 37 years old. Range: 19-91

Who are the right controls for a case-control study?

They have to be representative of the population where cases belong

Example of control selection

135 cases of *Cryptosporidium* hominis

- **Where?** City XX (population 350.000)
- **When?** Second week of September–first week of October 2020
- **Who?** 47% Women; mean age 37 years old. Range: 19-91

Source population:

People living at City XX > 19 years
Not travelled outside the city in the relevant period

How to select controls

- Random sample for population registry or list
  - Complete
  - Accesible
  - Feasible to stratify (sex, age, district….)

How to select controls

- Telephone / mobile register
- Challenges:
  - Who has a mobile?
  - Who will answer?

How to select controls

- Friends, family, neighbours
  - Can be efficient
  - Similar to cases
  - Low cooperation

How to select controls- Challenges

- Disease with high rate of asymptomatic
- Immune people
- 100% exposure

How to select controls

- Never perfect
- Balance strenghts and weaknessess
- Balance urgency, resources
- Defend your choices
- Take into account how limitations may affect results

Analytical studies- Case-control studies
Calculation of OR

- The odds ratio (OR) is the ratio between the probability that someone with disease has experience of the potential factor and the probability that someone without the disease has experience of the same factor
- Relative risk (RR) is used in cohort study and odds ratio (OR) is used in a case-control study

Odds ratio- Interpretation

- An OR = 1; no association

- An OR > 1; the study factor is a risk factor

- An OR < 1; the study factor is a “protective” factor

Case-Control study example

Outbreak context

- October 2004: Municipal medical officer in Bergen (Norway) alerted by the university hospital to an increase of patients with giardiasis
- During two weeks: 27 cases with unknown or no travel history
- Mainly young adults from the central part of the city
- 1–2 domestic cases of giardiasis are normally reported annually in Bergen

Nygård et al. (2006): A large community outbreak of waterborne giardiasis- delayed detection in a non-endemic urban area. BMC Public Health, https://doi.org/10.1186/1471-2458-6-141

Country example

Case-Control study example

The epidemiological investigation included:

- **Active case-finding, descriptive and ecological analysis**
  - Cases identified through the laboratory conducting giardia diagnostics in the area.
  - All laboratory-confirmed cases mapped based on address of residence
  - Attack rates and relative risks were calculated for each water supply zone.
- **Case control study**
  - Among people living in the central area of Bergen
  - Age- and sex matched controls randomly selected from the population register.

Nygård et al. (2006): A large community outbreak of waterborne giardiasis- delayed detection in a non-endemic urban area. BMC Public Health, https://doi.org/10.1186/1471-2458-6-141

Country example

Case-Control study example

Selection of controls and information collection

- Potential controls contacted by telephone (two controls per case)
- Cases and controls were asked about exposures two weeks before symptom onset for the case.
- Cases and controls that had travelled to a highly endemic country for giardiasis were excluded.
- Information was collected by telephone interviews
  - Structured questionnaire: food and drinks consumed different activities, clinical illness, use of health services
- Additional analysis to assess risk associated with quantity of water consumed
  - Group matched analysis including interviewed cases for whom we did not interview individually matched controls.
  - Group matching was based on gender and 10-year age groups.

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Country example

Case-Control study example

Matched univariate conditional logistic regression analysis of selected dichotomous risk factors among cases of giardiasis and matched controls, water-supply zone A, Bergen municipality 1/9 – 15/11 2004.

	Cases (%) (n = 27)		Controls (%) (n = 54)		Matched OR	95% CI	p-value
Having children in household	8	33%	17	34%	1.2	0.3 – 4.5	0.8
Having dog/cat	8	30%	7	13%	5.3	1.0 – 26.6	0.04
Salad	20	87%	45	90%	0.7	0.2 – 3.3	0.7
Tomato	19	83%	44	85%	0.8	0.2 – 3.2	0.8
Cucumber	20	83%	41	82%	1.2	0.3 – 4.3	0.8
Raw leek	9	38%	9	18%	7.1	0.9 – 58.9	0.1
Mineralwater	11	42%	27	51%	0.6	0.2 – 1.8	0.4
Coffee	18	72%	28	52%	2.4	0.7 – 7.9	0.2
Beer	8	33%	8	15%	3.3	0.9 – 12.7	0.06
Water at home (>5 glass)	20	74%	12	22%	7.3	2.4 – 21.8	<0.01
Water at the gym	10	38%	8	15%	5.2	1.1 – 26	0.03
Water in cafe or restaurant	10	38%	13	25%	1.8	0.6 – 5.2	0.3
Drinking water at work	14	56%	24	45%	1.6	0.6 – 4.4	1.6
Supermarket A	22	88%	27	55%	6.5	1.4 – 29.2	<0.01
Supermarket B	12	52%	19	40%	1.2	0.4 – 3.5	0.7

Nygård et al. (2006): A large community outbreak of waterborne giardiasis- delayed detection in a non-endemic urban area. BMC Public Health, https://doi.org/10.1186/1471-2458-6-141

Country example

Case-Control study example

Case- control study - Risk of giardiasis associated with quantity of water consumed among residents in water zupply zone A, Bergen municipality 1/ 9 – 15/11 2004. Group matched analysis by sex and 10-year age groups (83 cases, 54 controls).

Water intake	Cases	%	Controls	%	OR*	95% CI
< 1 glass	1	1 %	4	7 %	Ref	-
1 – 2 glasses	8	10 %	11	20 %	3.2	0.2 – 69.5
3 – 5 glasses	23	28 %	27	50 %	4.8	0.4 – 64.7
more than 5 glasses	51	61 %	12	22 %	7.4	1.2 – 44.5

* chi-square test for linear trend: 19.7; p < 0.001.

Nygård et al. (2006): A large community outbreak of waterborne giardiasis- delayed detection in a non-endemic urban area. BMC Public Health, https://doi.org/10.1186/1471-2458-6-141

In summary....

Descriptive epidemiology

What is happening?

Ecological epidemiology

Explore associations

Analitical epidemiology

Test hypothesis

Analytical studies

Small defined populations *Meetings, courses, restaurants, parties, weddings*

- Retrospective cohort study
- Relative risk

Large open populations *Cities, countries*

- Case control study
- Odds ratio

References

- This module is based on the document: *Surveillance and outbreak management of water-related infectious diseases associated with water-supply system*. Copenhagen: WHO Regional Office for Europe; 2019. Licence: CC BY-NC-SA 3.0 IGO.
- Additional used references are
  - Norwegian Institute of Public Health. Guidelines for investigation of outbreaks of food and waterborne diseases. Available at: https://www.fhi.no/globalassets/dokumenterfiler/rapporter/2018/guidelines-for-investigation-of-outbreaks-of-food--and-waterborne-diseases.pdf
  - Additional references were materials used in pilot national training workshops on water-related disease surveillance previously run by the World Health Organization Regional Office for Europe under the framework of the Protocol of Water and Health and training materials from the the European Programme for Intervention Epidemiology Training (EPIET)
- References used for the country examples are embedded in the presentation