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National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Sero-epidemiology of infe

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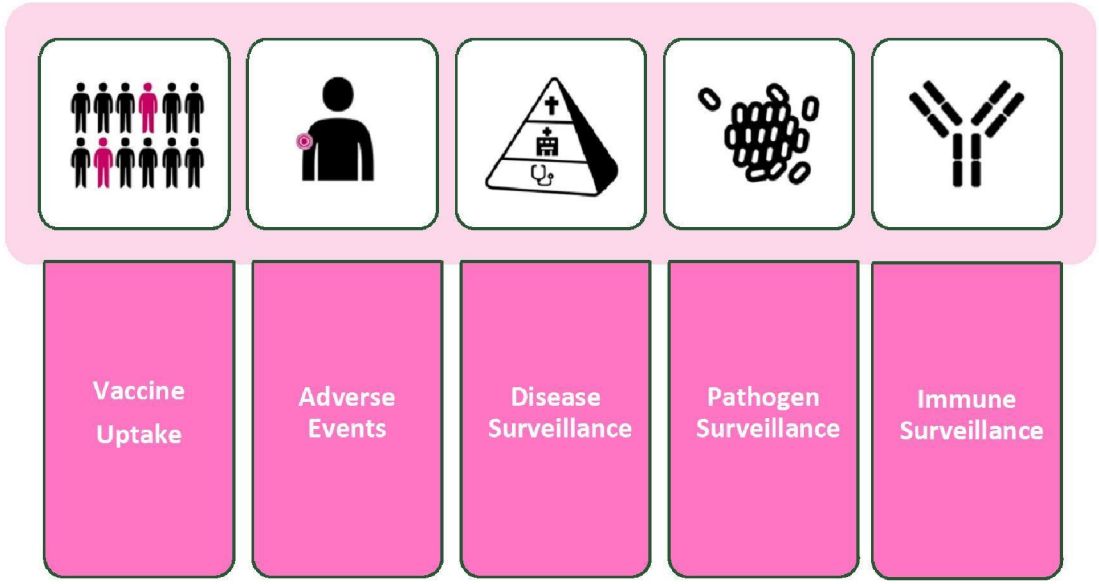
Course Infectious Diseases Utrecht - 19 October 2020

Today's lecture

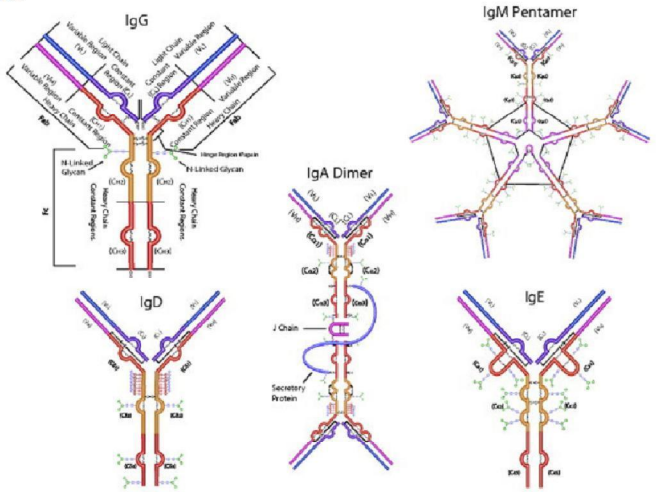
1) Pillars of infectious disease surveillance
2) Basic concepts in sero-epidemiology
3) Strengths and goals of sero-epidemiology
4) What is not covered (… a lot!)
5) Deterministic versus stochastic classification
6) Case Study – SARS-CoV-2 in the Netherlands

Surveillance of vaccine-preventable diseases



Basic concepts

- Prevalence versus incidence
- Susceptible, seronegative, seropositive, immune
- Vaccine efficacy versus vaccine effectiveness
- Vaccine-induced versus natural immunity
- IgG, IgM, IgA, IgE



Strengths and goals of sero-epidemiology

Sero-epidemiology offers an unbiased tool to study the dynamics of infection, uptake and effectiveness of vaccination in the population

Main goals:

1) What is the occurrence of an infection in the population?
2) Who is susceptible and who is immune in the population?
3) What has been the uptake of a vaccine?
4) How well are different groups protected against the infection?
5) Have the epidemiological dynamics changed over time?

Introduction of target disease into the NIP

1957	Diphtheria (D)
	Pertussis (Pe)
	Tetanus (T)
	Polio (Po)
1974	Rubella (R)
1976	Measles (Me)
1987	Mumps (Mu)
1993	*Haemophilus influenzae* type b (Hib)
2002	Meningococcal C (MenC) disease
2006	Pneumococcal (Pneu) disease
2009	Human papillomavirus (HPV)
2011	Hepatitis B (HepB)

The National immunisation program (NIP)

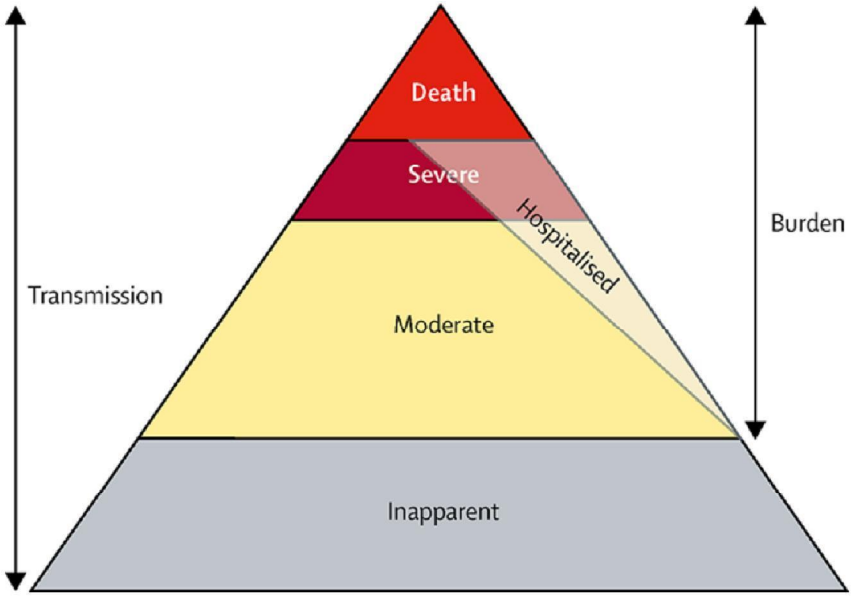
1) Monitoring for immunity against vaccine-preventable diseases present in the NIP

2) Tracking the dynamics of (infectious) diseases not (yet) included in the NIP

3) Monitoring for risk groups and for changes in immune status

4) Monitoring large outbreaks (Q-fever, legionella)

The infection-disease pyramid

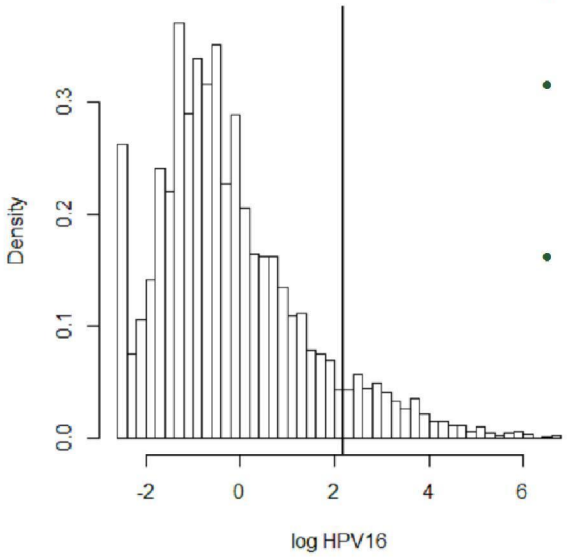


Lancet Respiratory Medicine (2017)

What is NOT covered today

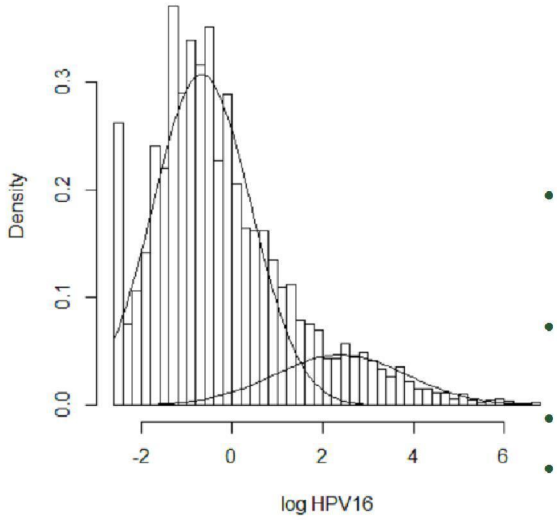
1) Sampling strategy to obtain a representative and sufficiently powered sample from the population
2) Comparison and biological basis of different tests (e.g., complement fixation, ELISA, multiplex)
3) Measurement error, dilution series, role of experimenter, batch differences, test validation, test characteristics
4) Structured data – longitudinal, multiple compartments, within and between groups, covariates, hierarchical protocols
5) Advanced methodological issues and practical implementation

The basics of classification – a motivating example



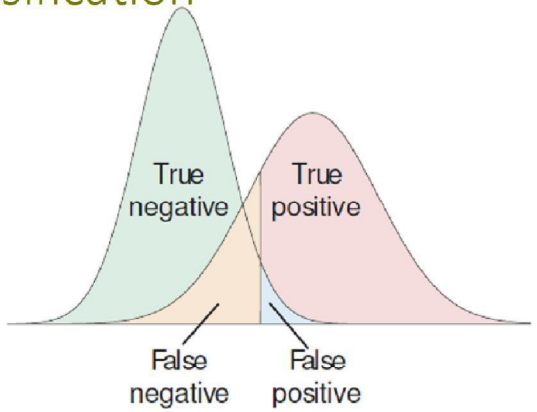
- Samples above the cut-off are classified as positive, and those below as negative
- Cut-off is usually based on ancillary data; ideally a gold standard against which a (sub)set of samples are compared
- Analysis usually proceeds by logistic regression, thereby
  - discarding information on the strength of the response
  - neglecting imperfect classification
  - Neglecting information on the ability to discriminate (strength of information)

The basics of classification



- Negative and positive outcomes are characterised by two distributions, thereby retaining the quantitative information of the strength of the responses
- Overlap of negative ands positive distributions - classification is not perfect!
- Enables probabilistic classification of samples
- Optimal cut-off can be derived
- Basis for analysis is a so-called binary mixture model

Basics of classification



		True status +	True status -
Test result	+	True pos	False pos
	-	False neg	True neg
		(Sens)	(Spec)

Basics of classification

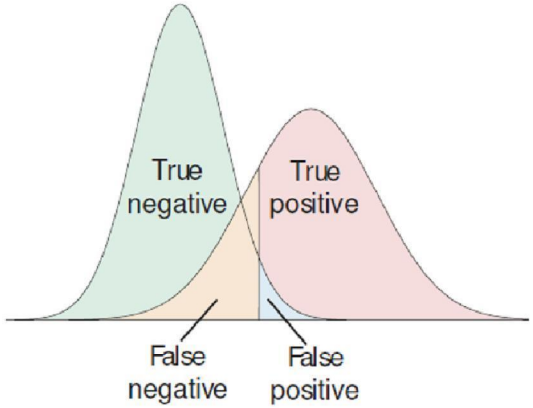
Sensitivity probability of a positive test (t_+) given a positive serum sample (s_+)

$$\text{Se} = P(t_+|s_+)$$

Specificity probability of a negative test (t_-) given the serum sample is negative (s_-)

$$\text{Sp} = P(t_-|s_-)$$

Basics of classification



$$\text{Sensitivity} = \frac{\#\text{ true positives}}{\#\text{ true positives} + \#\text{ false negatives}}$$

$$\text{Specificity} = \frac{\#\text{ true negatives}}{\#\text{ true negatives} + \#\text{ false positives}}$$

Apparent prevalence versus true prevalence

If the prevalence is p a positive test can be

- a "true" positive with probability $\text{Se} \times p$
- a "false" positive with probability $(1 - \text{Sp}) \times (1 - p)$

So that the probability of a positive test is

$$P(t_+) = \text{Se} \times p + (1 - \text{Sp}) \times (1 - p)$$

and the prevalence p can be calculated

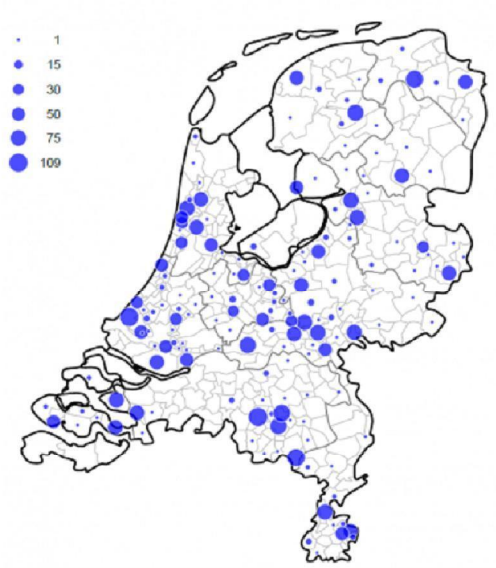
$$p = \frac{P(t_+) + \text{Sp} - 1}{\text{Se} + \text{Sp} - 1}$$

Case study: SARS-CoV-2 in the Netherlands

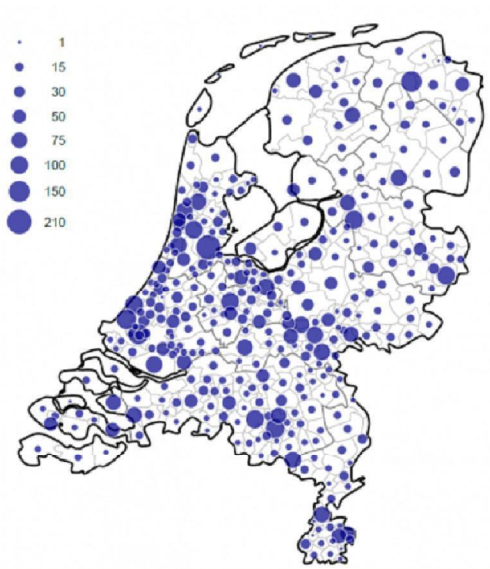
- Goals: study age-specific prevalence ('who has been infected up to now') and risk factors for infection
- Regular antibody testing of a representative sample of the Netherlands
- Round 1: April/May 2020, 3,200 samples
- Round 2: June/July 2020, 7,300 samples
- Round 3: September/October 2020, 7,000-8,000 samples
- Samples are analyzed with a multiplex immunoassay, enabling massive testing of multiple antigens on small volumes (fingerprick)

Case study: sampling

Round 1

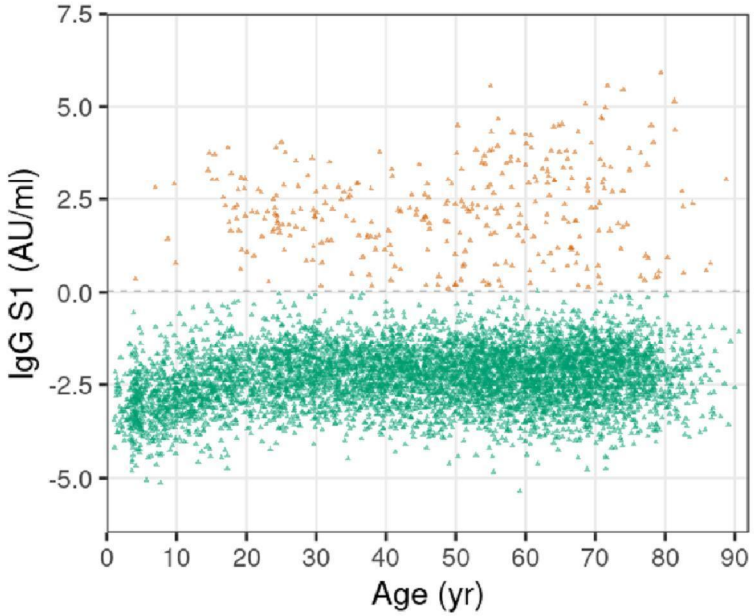


Round 2

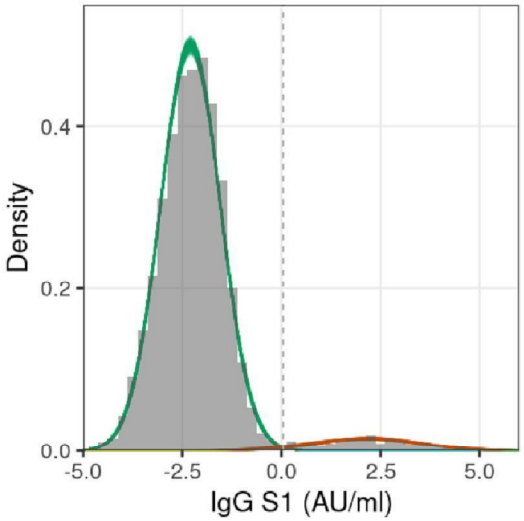


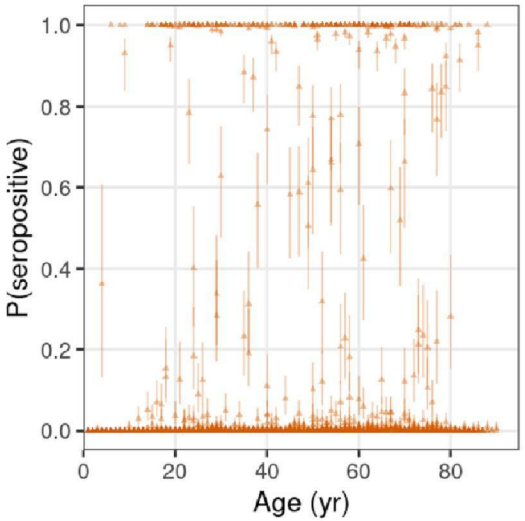
https://www.rivm.nl/pienter-corona-studie/resultaten

Case study: data

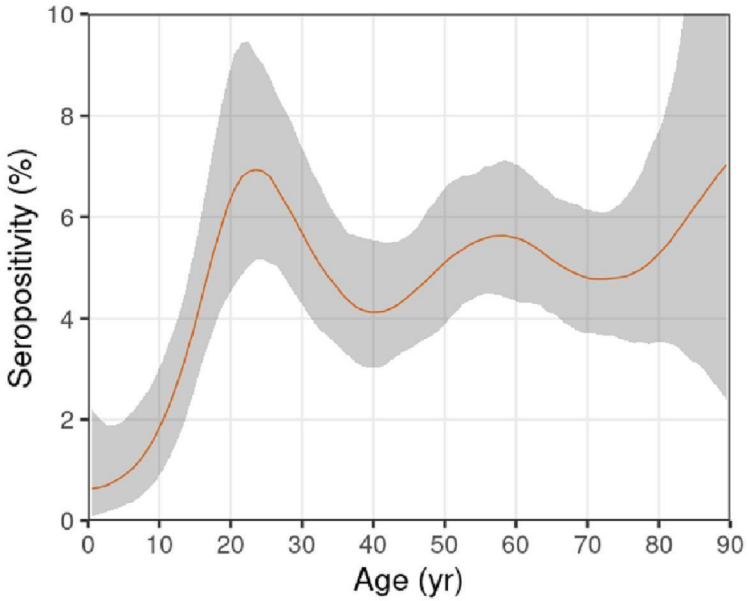


Case study: analysis

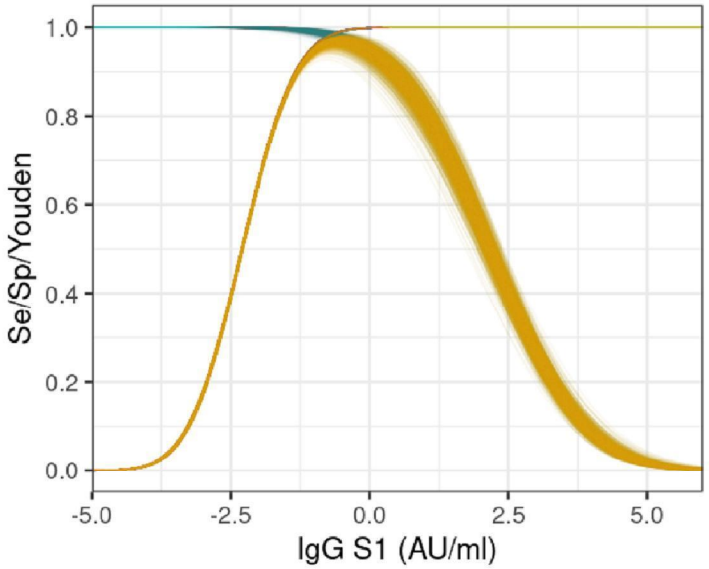




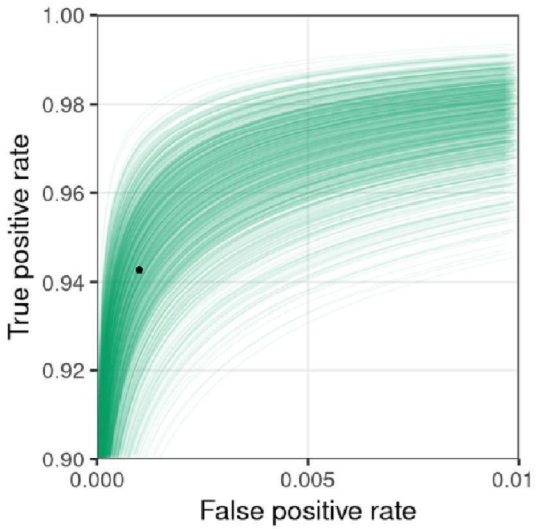
Case study: result



Case study: sensitivity, specificity, Youden index

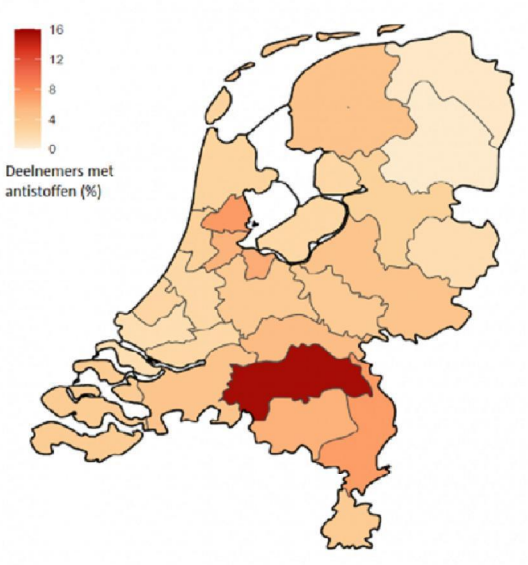


Case study: optimal cut-off



- Choice of cut-off does not only depend on test characteristics, BUT ALSO on the (expected) prevalence
- Prevalence is low (4-5%) so that high specificity is required
- We take Sp=0.999, with a cut-off of 0.04 AU/ml and implied Se=0.94 (95%CrI: 0.91-0.97)

Case study: stratification by Municipal Health Service



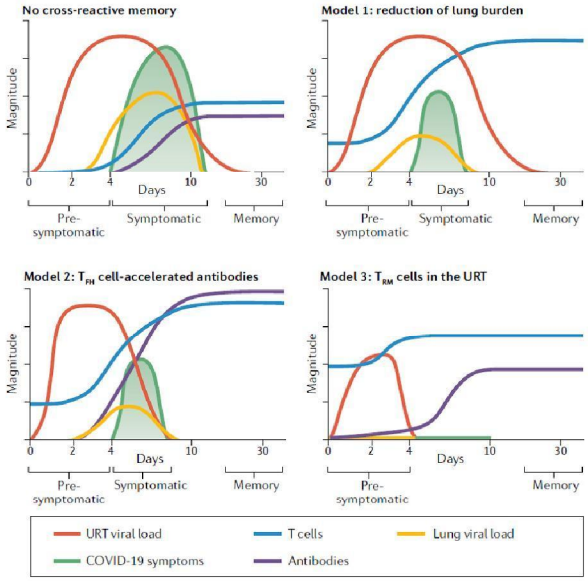
- Estimated prevalence in June/July 2020 was substantially higher the southeast of the Netherlands than in other regions
- Third round is expected to show a shift of higher prevalence in highly urbanized areas

Case study: risk factors for infection

Klacht	Seropositief	Seronegatief	Totaal
Hoofdpijn	64,9%	32,6%	33,3%
Loopneus	60,8%	36,7%	37,3%
Hoesten	60,8%	29,5%	30,2%
Gewrichtspijn	56,8%	16,2%	17,1%
Verlies van geur en/of smaakvermogen	52,7%	3,6%	4,8%
Algehele malaise	46,0%	10,8%	11,6%
Keelpijn	44,6%	26,0%	26,4%
Koorts	43,2%	11,8%	12,5%
Spierpijn	29,7%	10,5%	10,5%
Diarree	24,3%	12,6%	12,9%
Prikkelbaarheid / verwarring	23,0%	7,6%	7,9%
Buikpijn	17,6%	11,9%	12,0%
Kortademigheid	17,5%	8,2%	8,4%
Misselijkheid / overgeven	17,6%	6,7%	7,0%

- Analyses of risk factors for infection are ongoing, and these include demographic, socio-economic, household composition, and putative risk factors for infection

Case study: perspective



- How long will antibody levels persist?
- Do high antibody levels correlate with immunity and low probability of re-infection. And what about severity of disease?
- Relation with T-cell dynamics may well prove crucial

Nature Reviews Immunology (2020)

Case study: discussion

- Unbiased estimates of infection rates are crucial for reliable epidemiological assessments (How many persons have been infected? Are there differences in attack rates between age groups? Who is at increased risk of infection?) and can only be obtained with sero-epidemiology

- Likewise, estimates of hospitalization rates and infection fatality rates can only be obtained from sero-epidemiological studies

- Regular updates of the Dutch serological studies are posted on https://www.rivm.nl/pienter-corona-studie/resultaten

Acknowledgments

- (10)(2e)
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- The Corona sero-epidemiology team, ao (10)(2e), (10)(2e), (10)(2e), (10)(2e), (10)(2e), (10)(2e)