WOAH AMR training 2026
Rakuno Gakuen University

Veterinary Epidemiology 2

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WOAH Collaborating Centre
for Food Safety

World Organisation
for Animal Health
Founded as OIE

Screening

- Purpose
  - To screen out the individuals with high risk of a disease from apparently healthy population
  - Early detection is effective
    - For diseases which have severe symptoms, but the probability of cure is high if the treatment is provided during the early phase
    - For infectious diseases that spread into wide areas through emission of large number of the pathogen before the hosts show clinical sign

Indicators of diagnostic test validity

		True status		Total
		Infected	Non-infected	
Test results	Positive	a	b	a+b
	Negative	c	d	c+d
	Total	a+c	b+d	a+b+c+d

False positives

False negatives

Sensitivity: probability of truly diseased individuals that are diagnosed positive
a/(a+c)

Specificity: probability of truly non-diseased individuals that are diagnosed negative
d/(b+d)

Positive predictive value: probability of positively diagnosed individuals are diseased
a/(a+b)

Negative predictive value: probability of negatively diagnosed individuals are not diseased
d/(c+d)

Trade off relationship between sensitivity and specificity

- Shifting cut off line toward left ⇒ sensitivity↑, specificity↓
- Shifting cut off line toward right ⇒ sensitivity↓, specificity↑

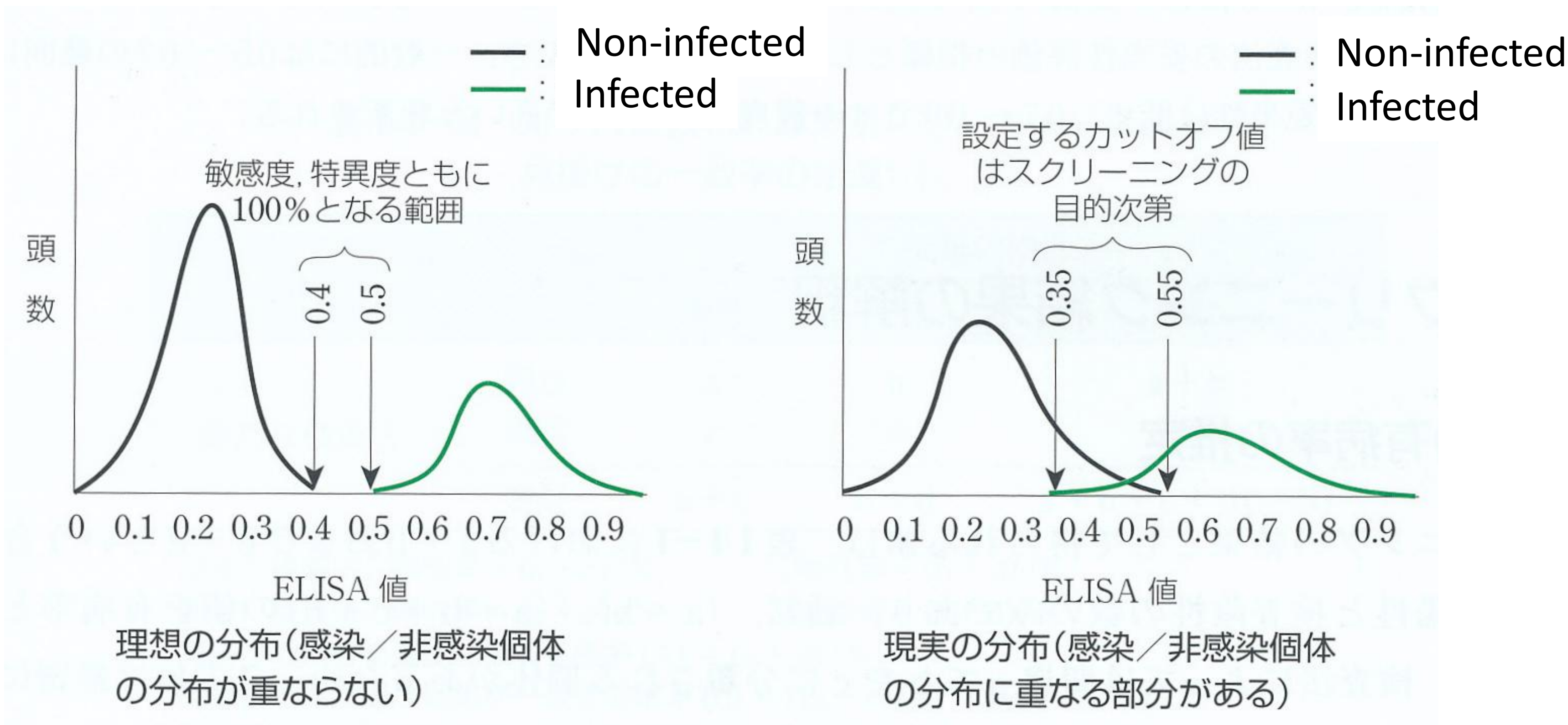


図 **14−1** 敏感度と特異度の関係(トレードオフ)

Receiver operating characteristic curve (ROC)

Better diagnostic tool
Curve goes through closer to the top left corner

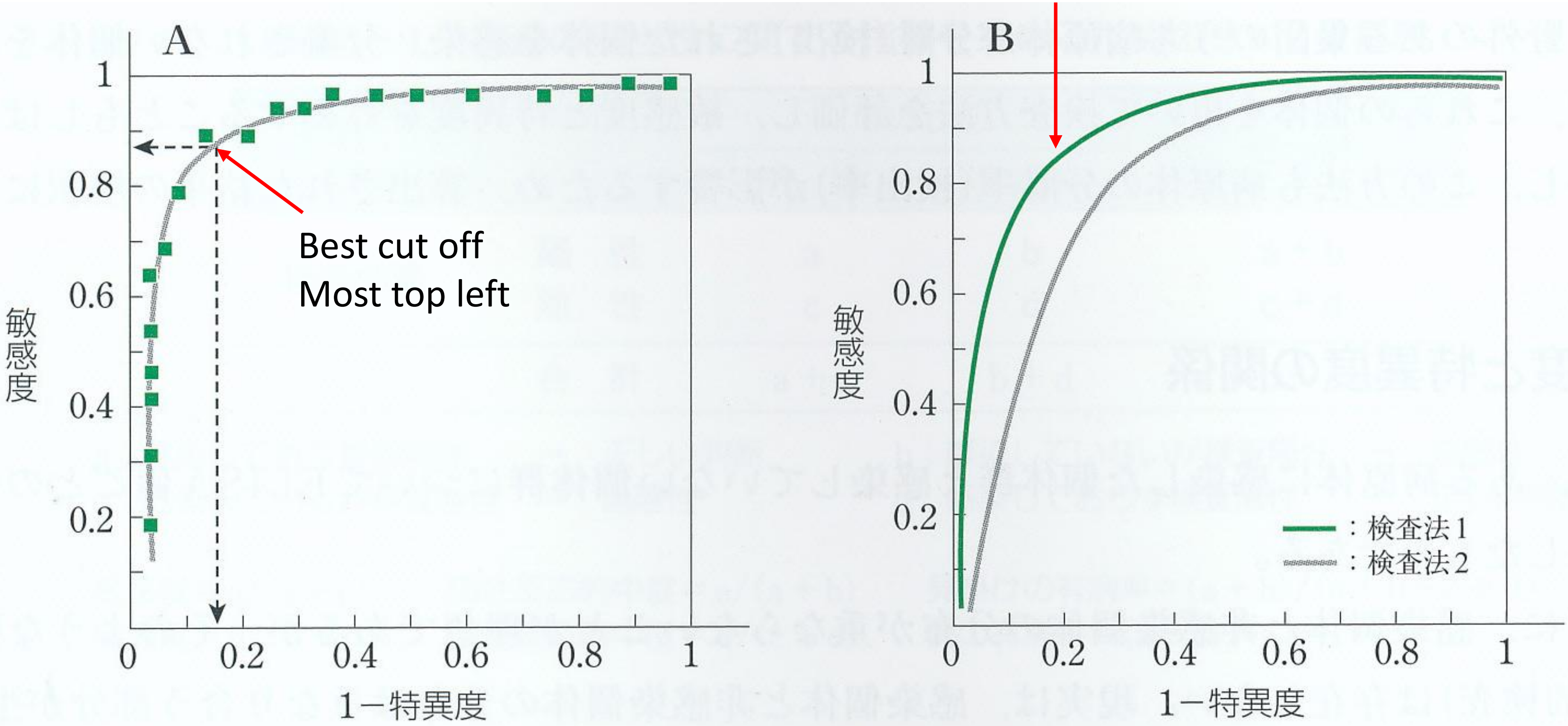
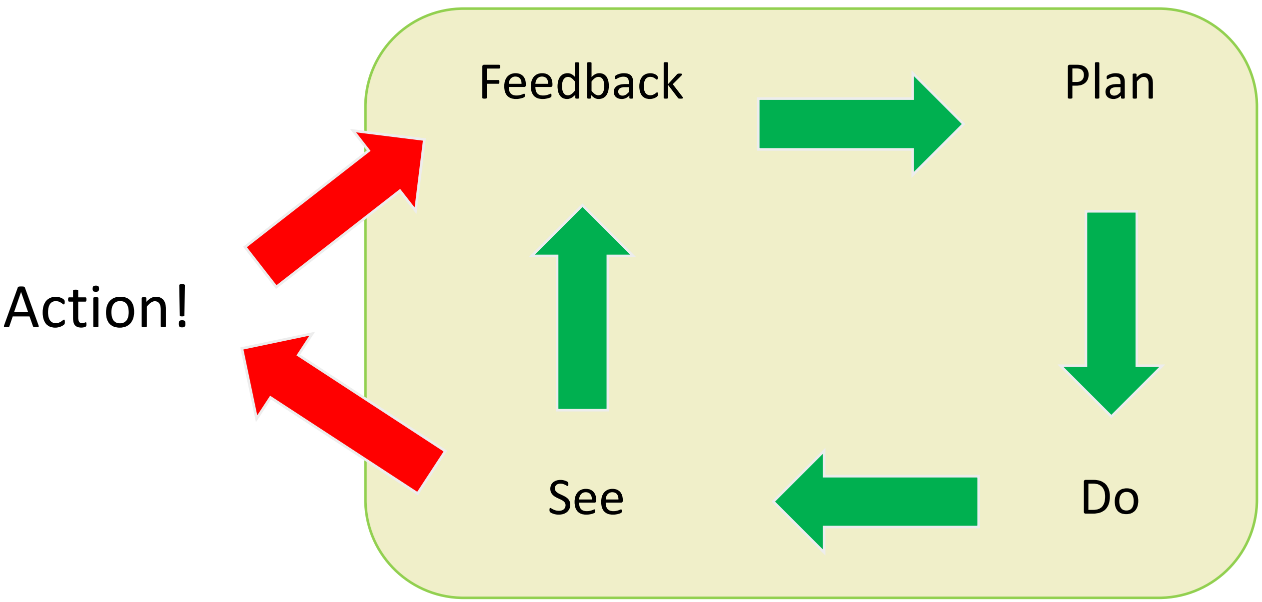


図14−2　ROC曲線とその利用

Surveillance

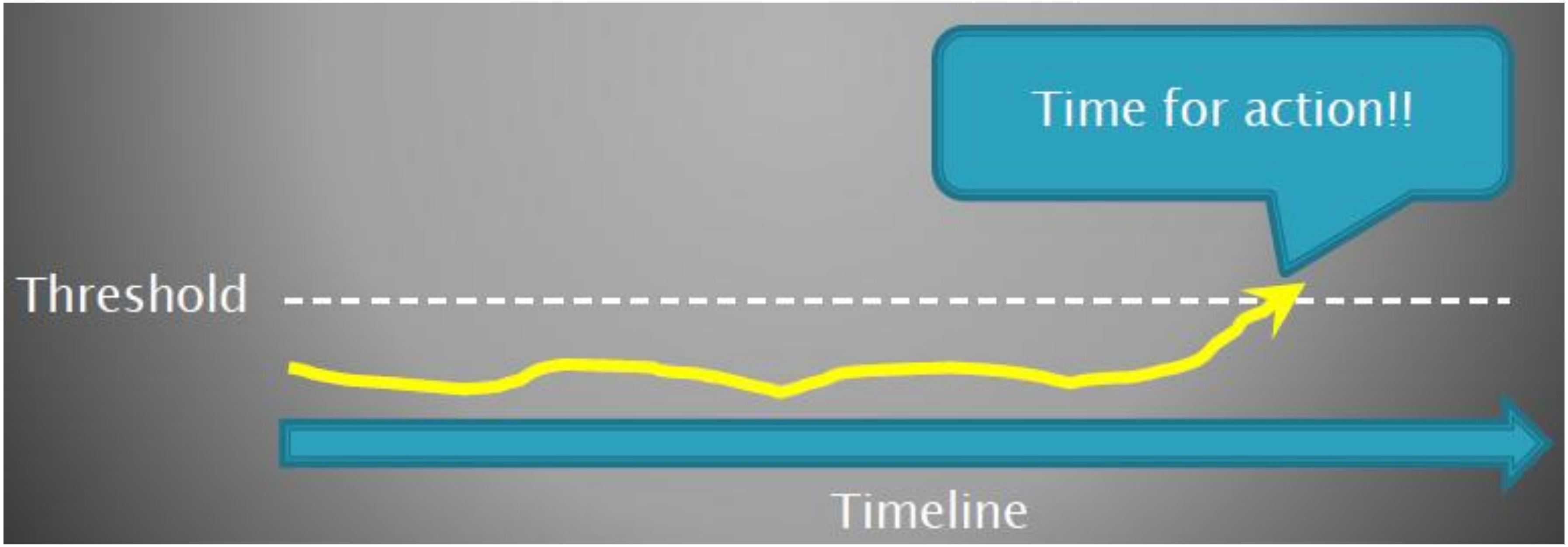
- Systematic and continuous collection, analysis, and interpretation of data, closely integrated with the timely and coherent dissemination of the results and assessment of those who have the right to know so that action can be taken



* Surveillance should not be confused with a survey, which is to collect information.

Another definition of surveillance

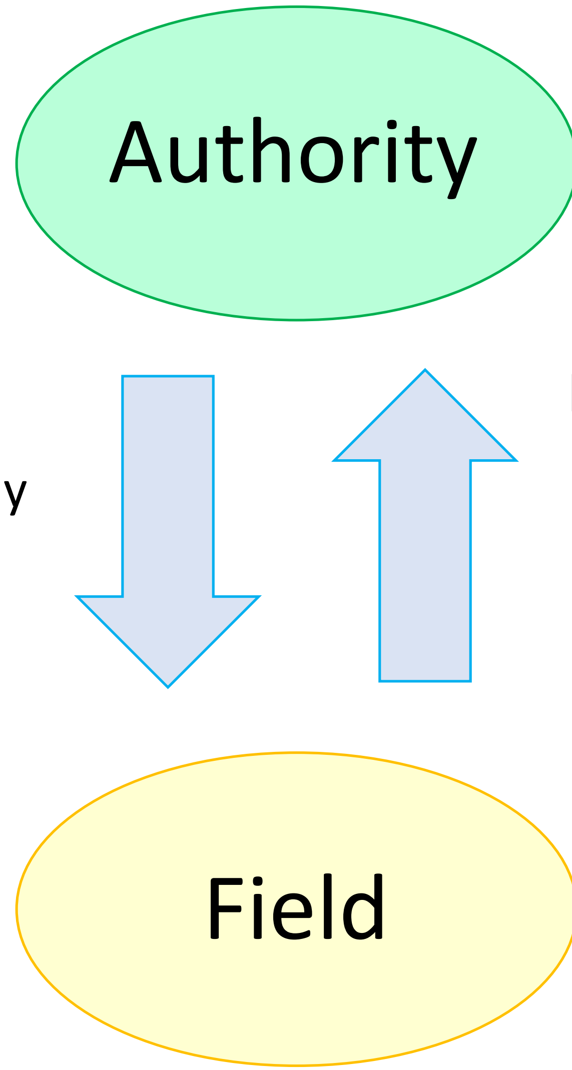
- Continuous collection, analysis, and feedback of data so that action can be taken when prevalence or incidence exceeded the threshold



Five components of surveillance

- Continuous collection of information and evaluation
- Clear definition of target population
- Clear definition of a case (diagnostic criteria)
- Timely publication of information
- A survey or application of information to control the emerged disease

Types of surveillance



Active surveillance

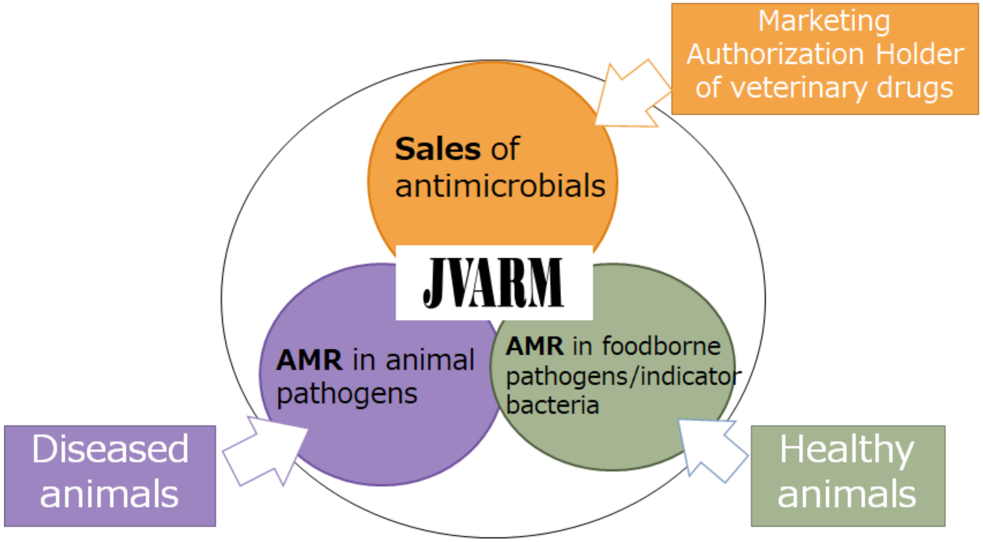
・Veterinary authority actively collects information for a specific purpose

Passive surveillance

・Based on reports

Monitoring

- The intermittent performance and analysis of measurements aimed at detecting changes in the health status of populations or in the physical or social environment.
- **Surveillance is ‘continuous’ and involves action.*



*AMR: antimicrobial resistance

Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM)

Response of the world against Swann Report

Transparency, prudent use, and risk assessment

1969
Swann Report

Gradual AMU reduction as a growth promoter in EU in 1999-2006. Ban in 2006.

UK

1971
Ban of penicillin and tetracycline use in feeds. Antimicrobial use in animals increased.

1993
Approval of FQ in chicken feed. Sharp increase in FQ resistant *Salmonella* in humans.

2007
Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI)

Sweden

1986
Ban of antimicrobials as a growth promoter.

1995
Joined in EU.
Requesting rigorous AMU control to EU.

2000
Swedish Veterinary Antimicrobial Resistance Monitoring (SVARM)

Denmark

1995
Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP)
Ban of avoparcin associated with vancomycin resistance.

USA

1996
National Antimicrobial Resistance Monitoring System (NARMS)

2000
FDA quantitative risk assessment for FQ resistant *Campylobacter* in chicken. FQ was banned in 2005.

Japan

1973
Discovery of R plasmid

1976
Distinguishing feed additive antimicrobials from feed additive

Treatment

Growth promoter

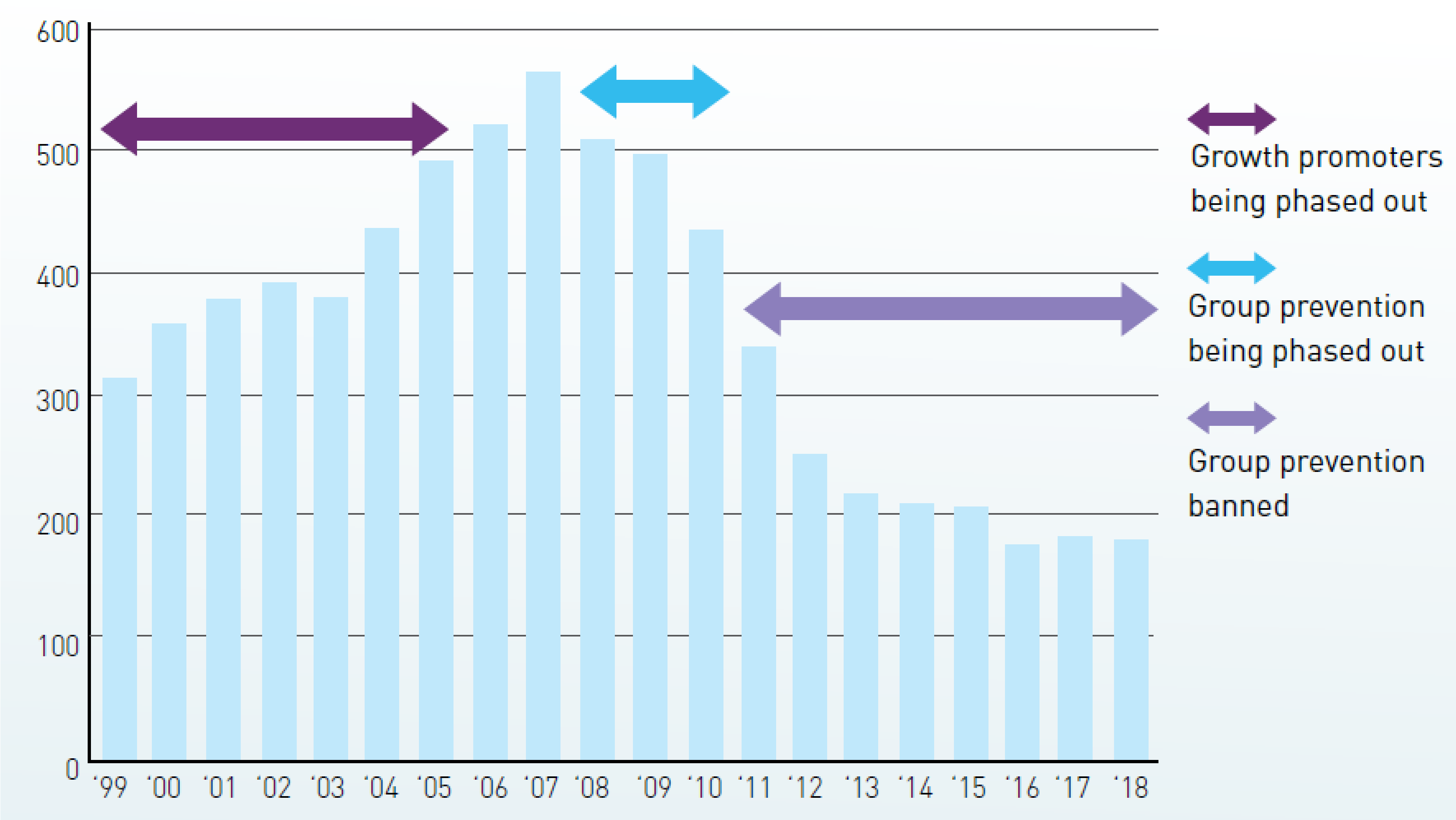
1976-1977, 1992-1994
MAFF nation-wide AMR study

1997
Ban of orienticin associated with vancomycin resistance.

1999
Japan Veterinary Antimicrobial Resistance Monitoring System (JVARM)

The effect of regulating AMU as a growth promoter (the Netherlands)

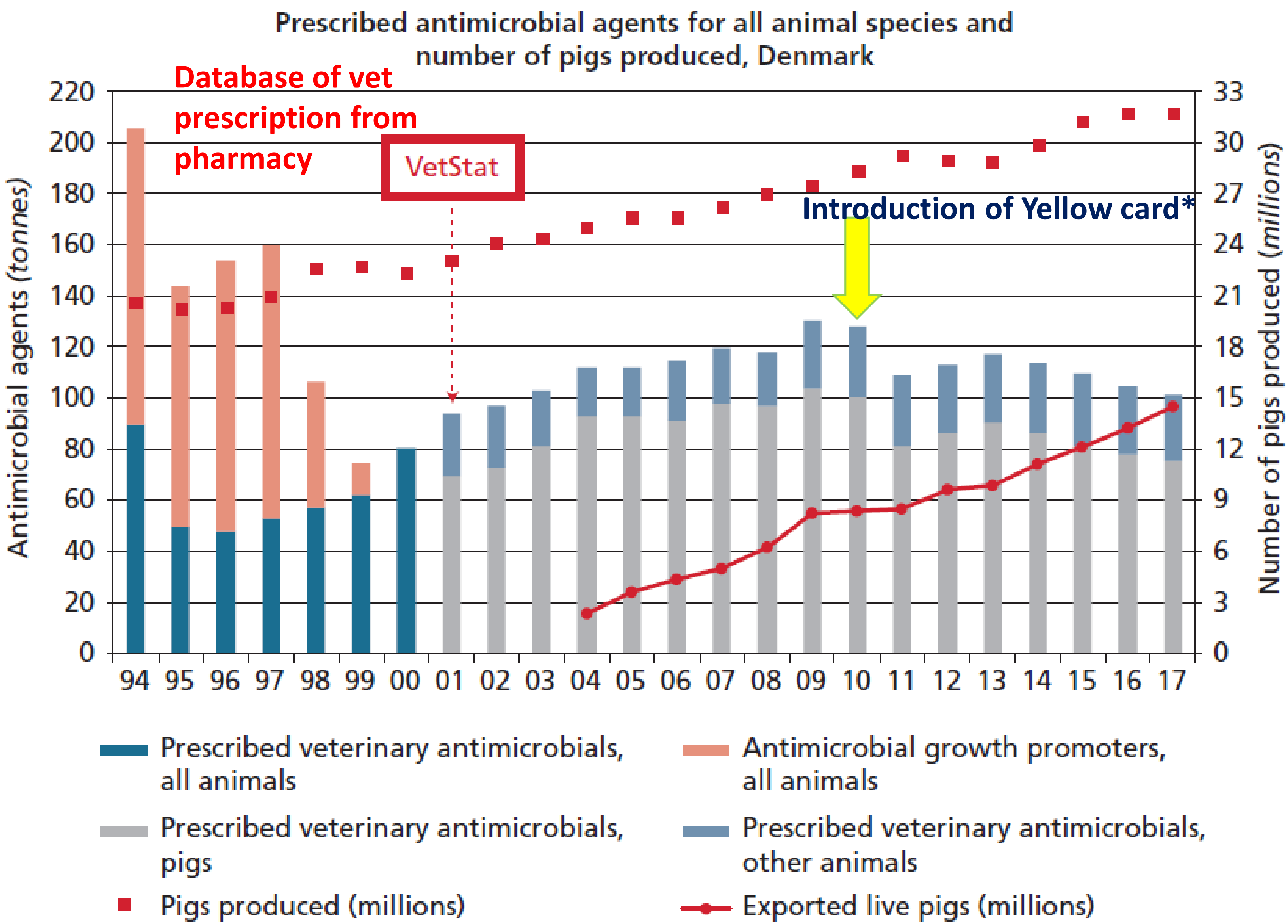
Dutch farm antibiotic sales, 1999 to 2018 (tonnes of active ingredient)



Alliance to save our antibiotics. 2019. “Swann song” for routine antibiotics use, 50 years on?

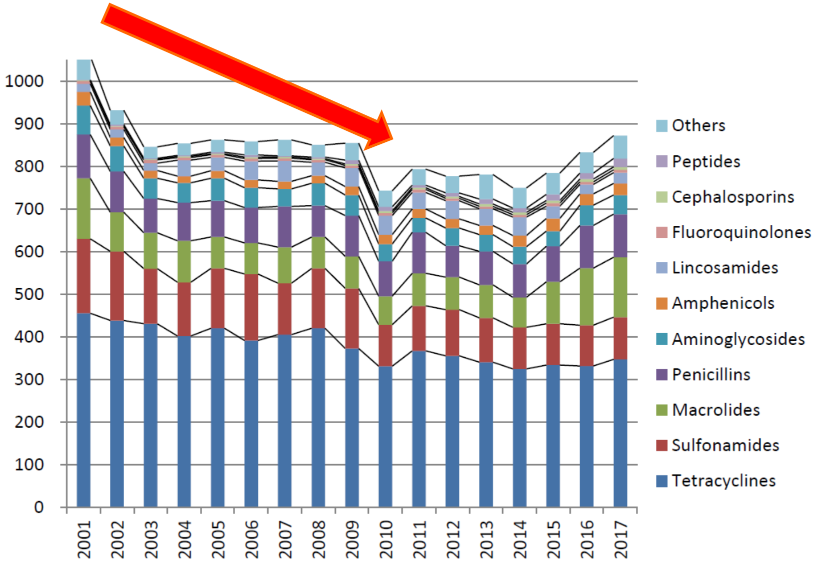
Success of Denmark

Yellow card scheme*
In case AMU is high,
- **Regulation of oral AMU**
- **Mandatory vet guidance and cost share**



FAO and Danish Veterinary and Food Administration. 2019. Lessons learned in Denmark.

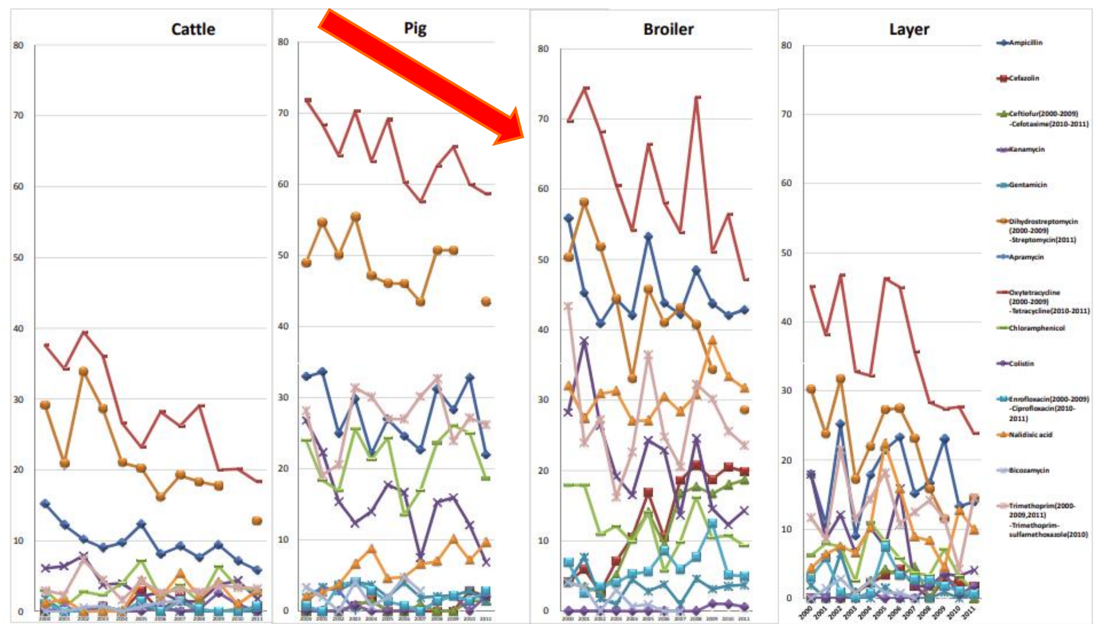
The changes in the sales of veterinary antimicrobials and resistance rates in Japan



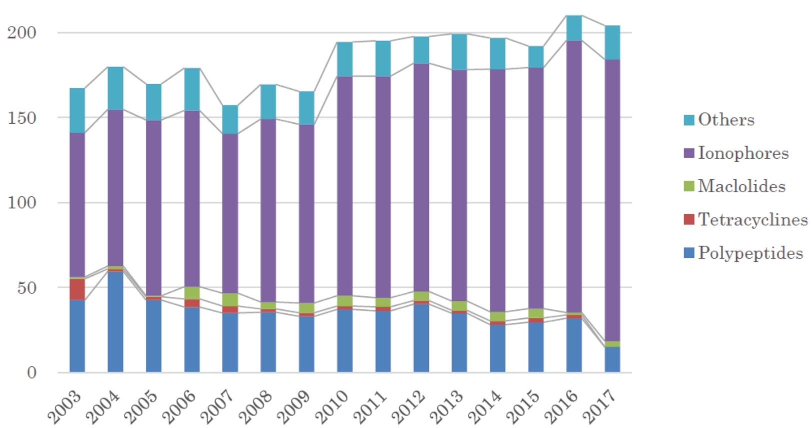
動物用抗菌薬販売量の推移（t）JVARM報告書

Significant reduction on resistance rates in *E. coli* between 2000 and 2011

Fig.7 Resistance(%) in *Escherichia coli* isolates from animals (2000–2011)

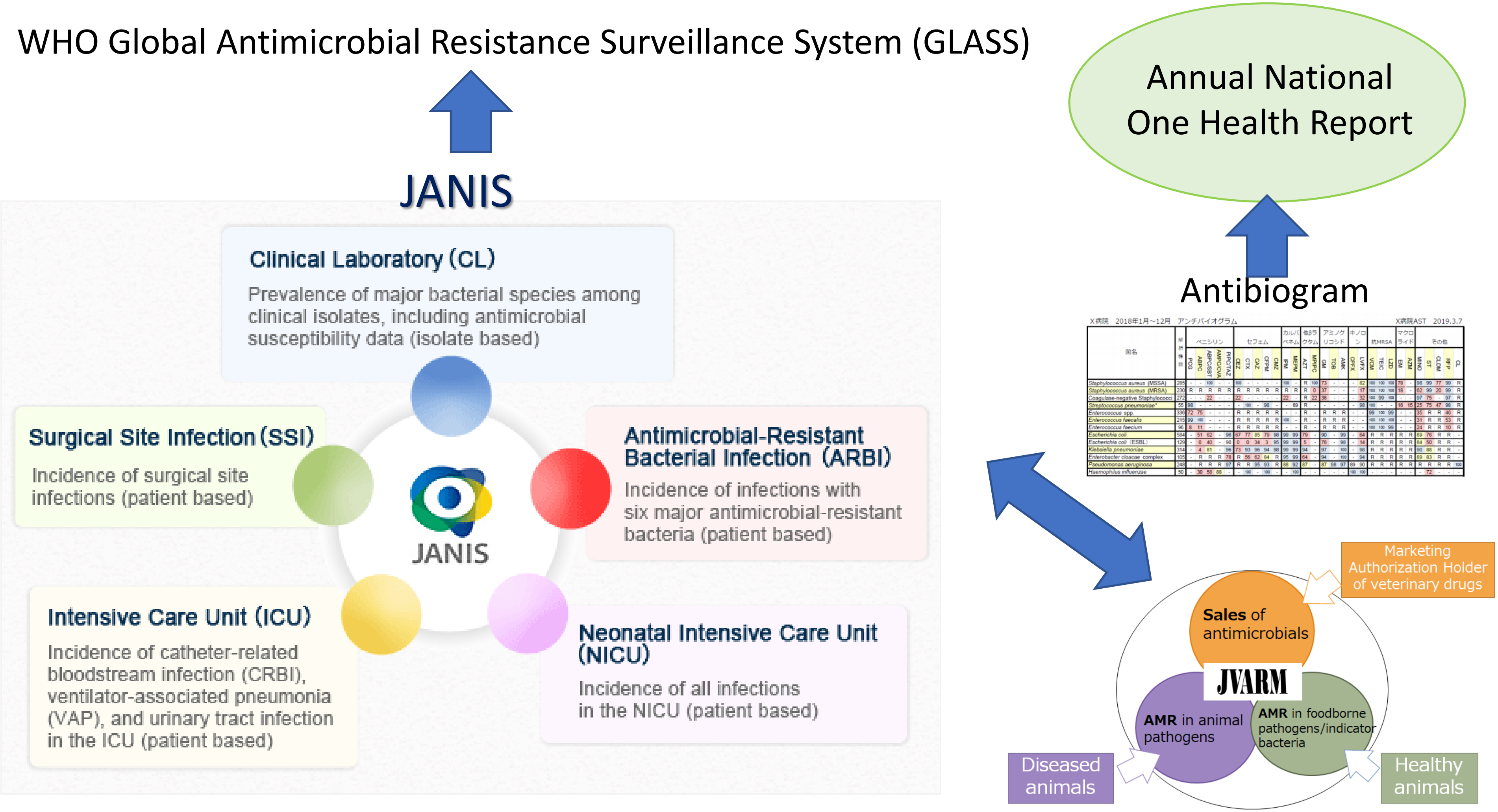


JVARM Report (2000-2011)



飼料添加物販売量の推移（t）JVARM報告書

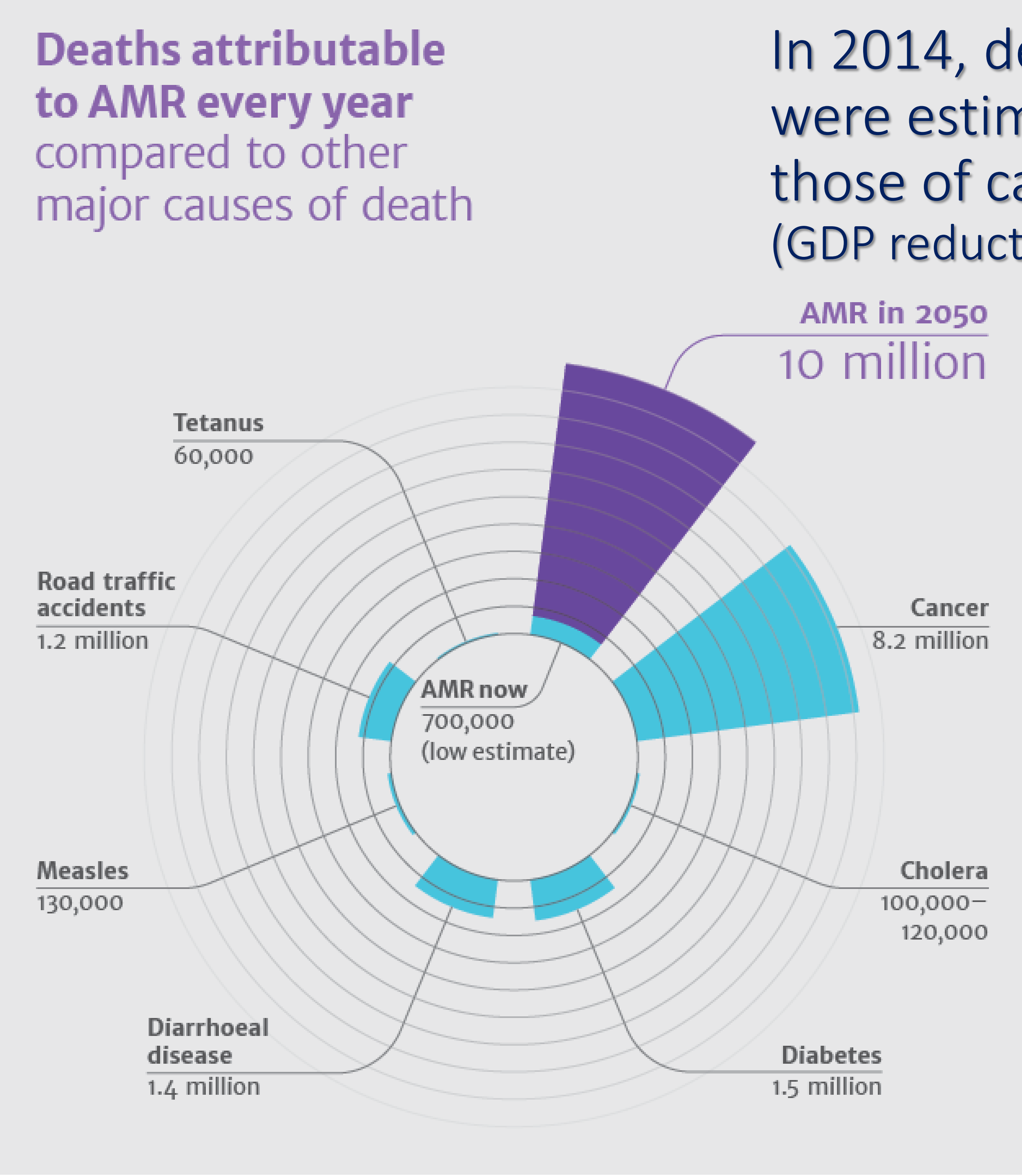
Japan Nosocomial Infections Surveillance (JANIS)



*AMR: antimicrobial resistance

In 2014, deaths due to AMR were estimated to excess those of cancer in 2050

(GDP reduction by 2-3.5%)



Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations.
The Review on Antimicrobial Resistance, Chaired by Jim O'Neill. 2014. UK.

In 2015

- to improve awareness and understanding of antimicrobial resistance through effective communication, education and training;
- to strengthen the knowledge and evidence base through surveillance and research;
- to reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures;
- to optimize the use of antimicrobial medicines in human and animal health; and
- to develop the economic case for sustainable investment that takes account of the needs of all countries and to increase investment in new medicines, diagnostic tools, vaccines and other interventions.

Basic statistics in veterinary epidemiology

The aims to achieve

- To be able to explain types of data, test statistics and distribution

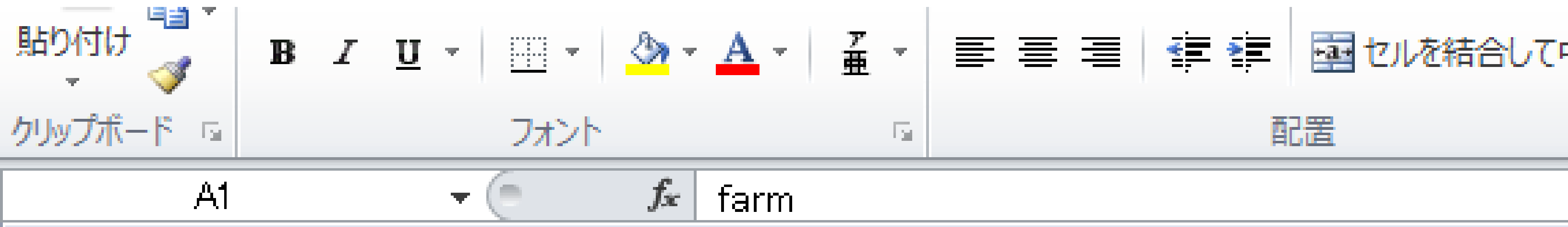
- To be able to understand and apply estimation and tests
  - Hypothesis testing
  - Tests for means
  - Tests for proportions
  - Tests for relationships between variables

Types of data

- Quantitative data
  - Presented with numbers
  - Age, body weight, blood pressure, biochemistry test values (continuous variable)
  - Daily case count, white blood cell count, somatic cell count, the number of animals (count variable)
  - Rank

- Qualitative data
  - Status or attribution to categories
  - Sex, infection status, exposure status (binary variable)
  - Breeds, city/town names, and sociological attribution (categorical variable)

Data storage
Farm level data



farm	dipping	teat_dis	stall	sapos	saneg
A	k	sz	t	11	91
B	k	sz	f	38	201
C	b	sk	t	4	95
D	b	sz	t	1	70
E	b	sz	t	13	72
F	k	sk	t	19	85
G	b	sk	f	2	81
H	b	sk	t	13	116
I	k	na	t	21	120

Category

The numbers of cows

Data storage
Individual animal level data

farmer	cow	teat	SA	dip	dis	stall
A	A108	A108a	0	b	sz	t
A	A108	A108b	0	b	sz	t
A	A108	A108c	0	b	sz	t
A	A108	A108d	0	b	sz	t
A	A114	A114a	1	b	sz	t
A	A114	A114b	0	b	sz	t
A	A114	A114c	0	b	sz	t
A	A114	A114d	0	b	sz	t
A	A120	A120a	1	b	sz	t
A	A120	A120b	0	b	sz	t
A	A120	A120c	0	b	sz	t
A	A120	A120d	0	b	sz	t
B	B121	B121a	1	b	sz	t
B	B121	B121b	1	b	sz	t
B	B121	B121c	0	b	sz	t
B	B121	B121d	0	b	sz	t
B	B128	B128a	0	b	sz	t
B	B128	B128b	0	b	sz	t
B	B128	B128c	0	b	sz	t
B	B128	B128d	0	b	sz	t
C	C132	C132a	0	b	sz	t
C	C132	C132b	0	b	sz	t
C	C132	C132c	0	b	sz	t
C	C132	C132d	0	b	sz	t

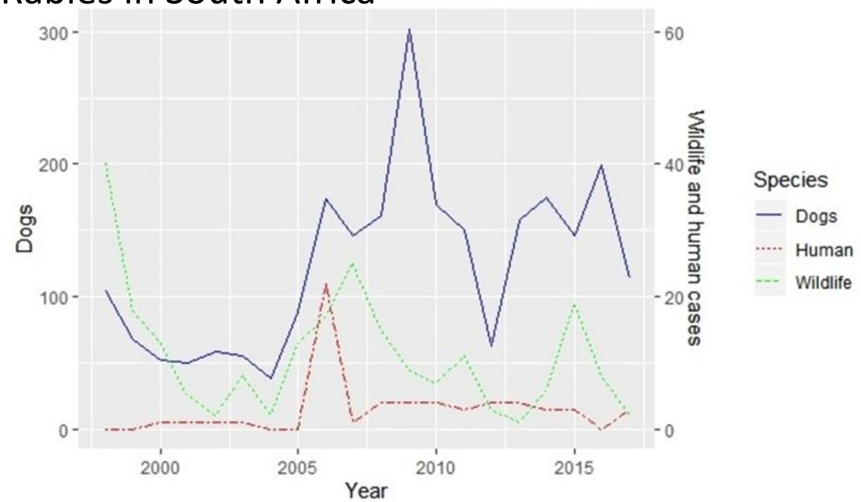
Binary data/count data
(The number of mastitis occurrence)

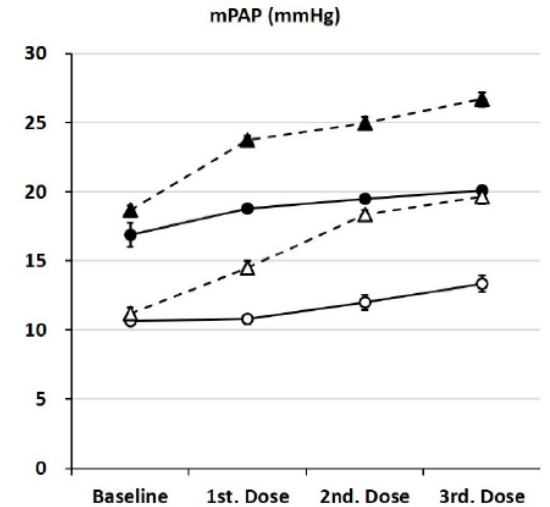
Left front/ left rear/ right front/ right rear

Data observation

-Your eyes can tell hypotheses-

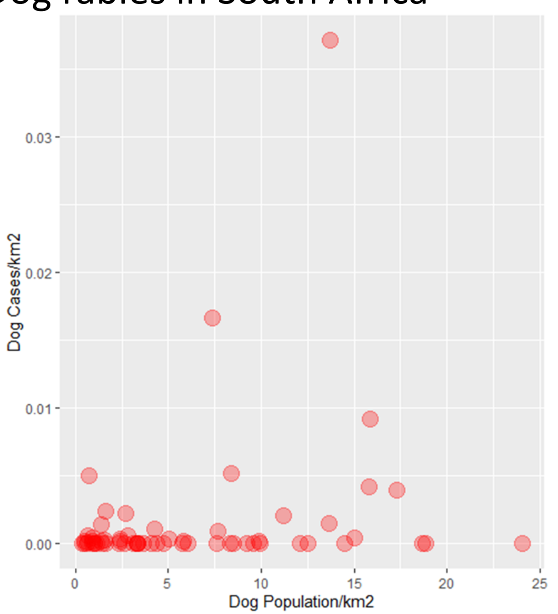
Rabies in South Africa

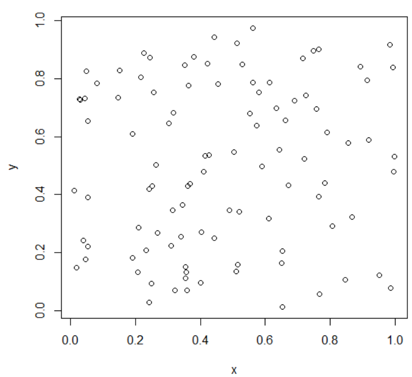


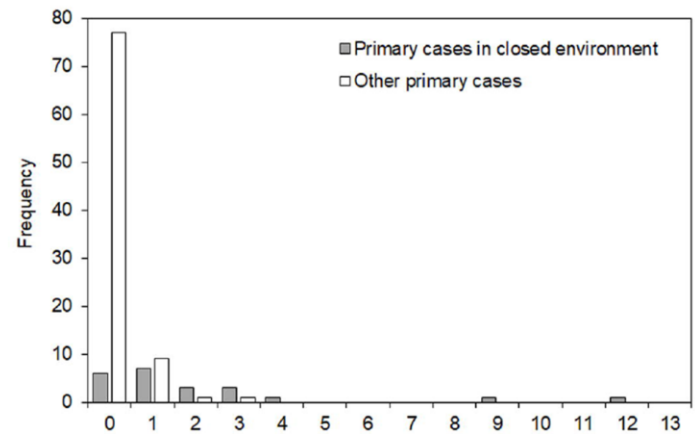


The effects of colforsin and dobutamin on mean pulmonary artery pressure in normal and acidic conditions (Itami and Makita et al. PLOS ONE 2020)

Dog rabies in South Africa







Nishiura et al. 2020. The numbers of secondary cases in Covid 19

Normal distribution

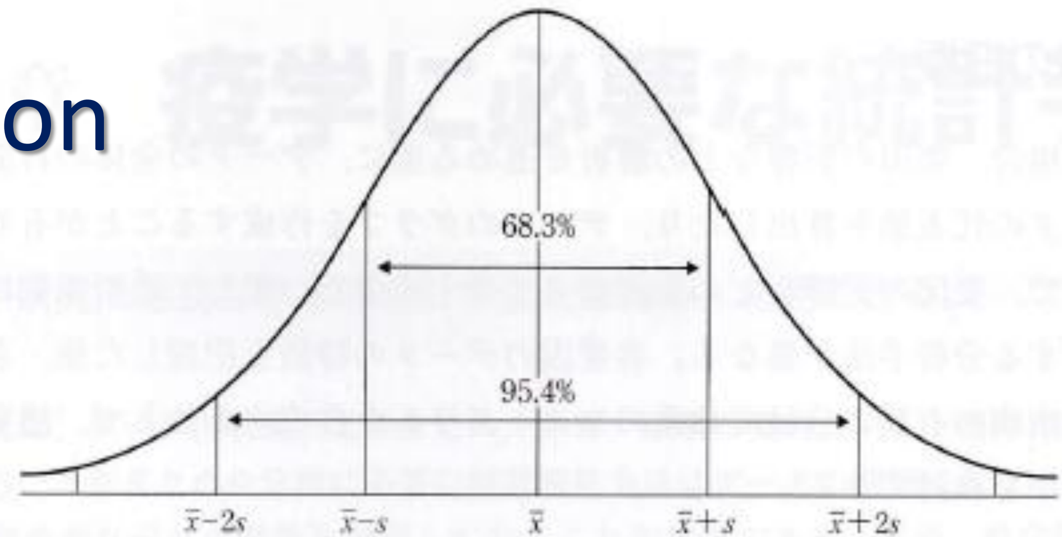
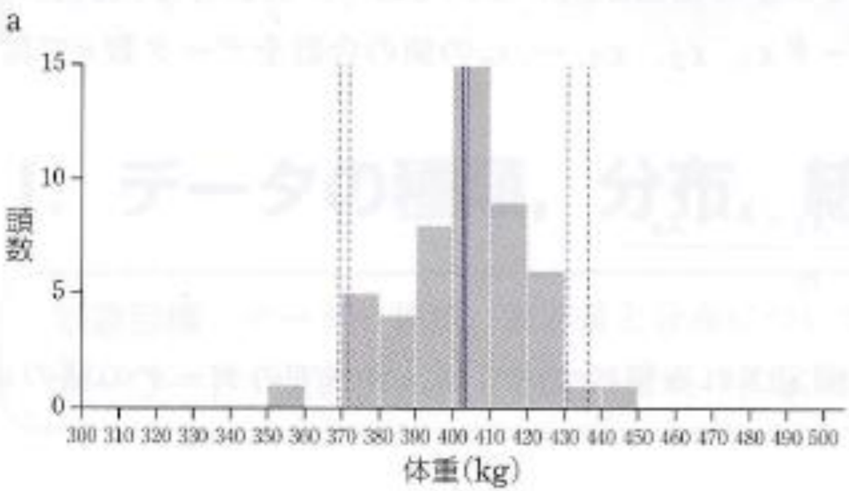
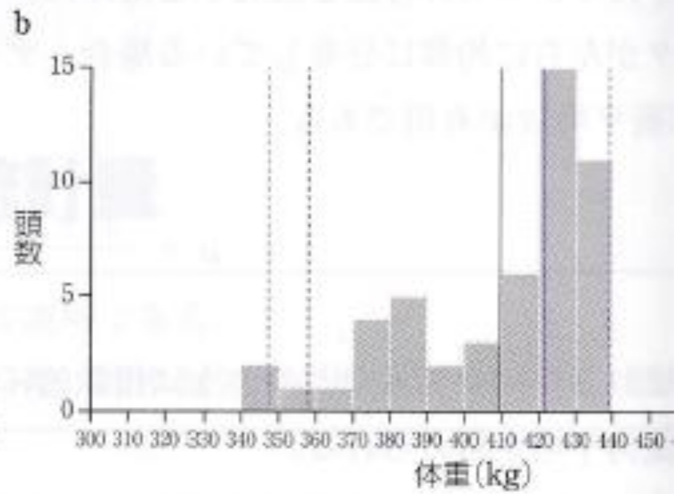


図10-1　正規分布の平均と標準偏差の関係



Data following normal distribution



Data not following normal distribution

Visualizing data

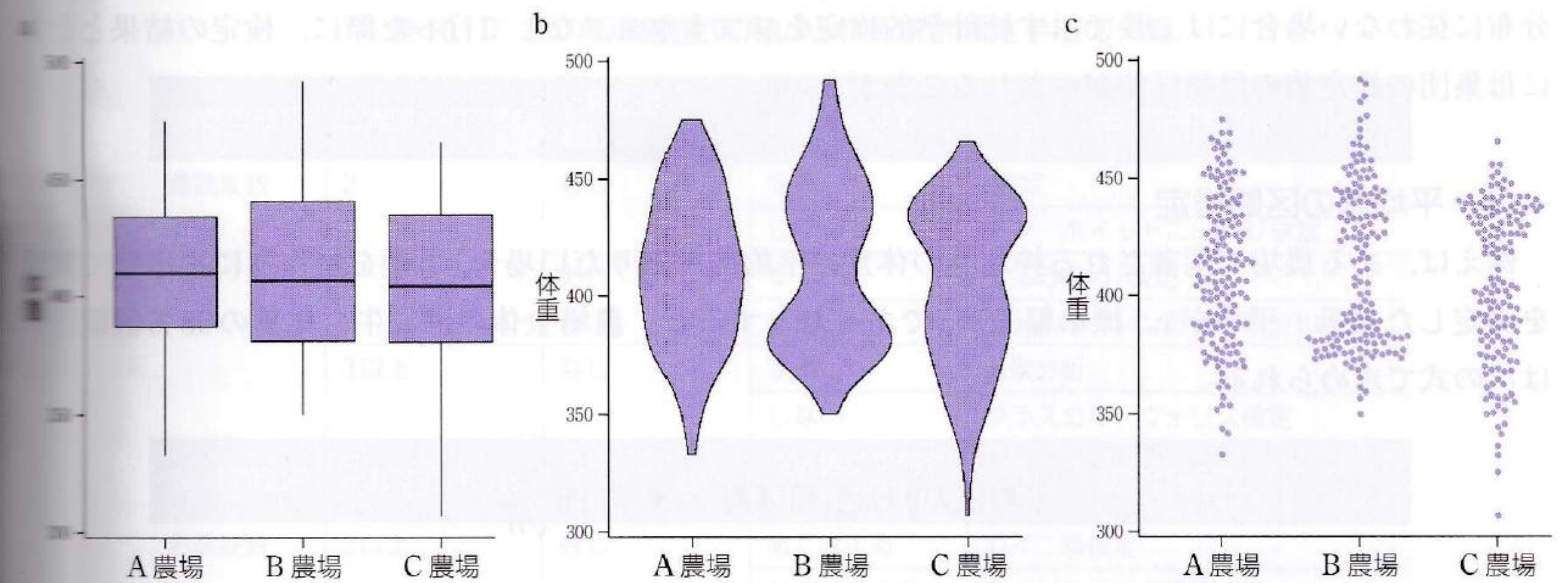


図10-3 各農場の動物の体重分布図を箱ひげ図(a), バイオリンプロット(b)およびビースウォームプロット(c)で表した

Description of the characteristics of data

- Example
  - In a cattle herd, birth body weights of 30 calves were measured.
  - Can you tell the mean by just an observation?

30.6	30.1	29.3	26.7	29.8
26.8	29.9	29.4	28.9	28.3
28.1	27.2	26.8	29.0	29.7
28.8	29.1	29.8	27.4	28.6
30.6	29.0	31.0	28.0	27.2
29.8	28.4	31.2	29.7	29.2

(単位kg)

Description of the characteristics of data

- Yes, your eyes have a quantitative sense!
  - Mean: 28.9 kg
  - Standard deviation: 1.3 kg

```
> attach(calfBW)
> names(calfBW)
[1] "BW"
> sd(BW)
[1] 1.2591
> mean(BW)
[1] 28.94667
```

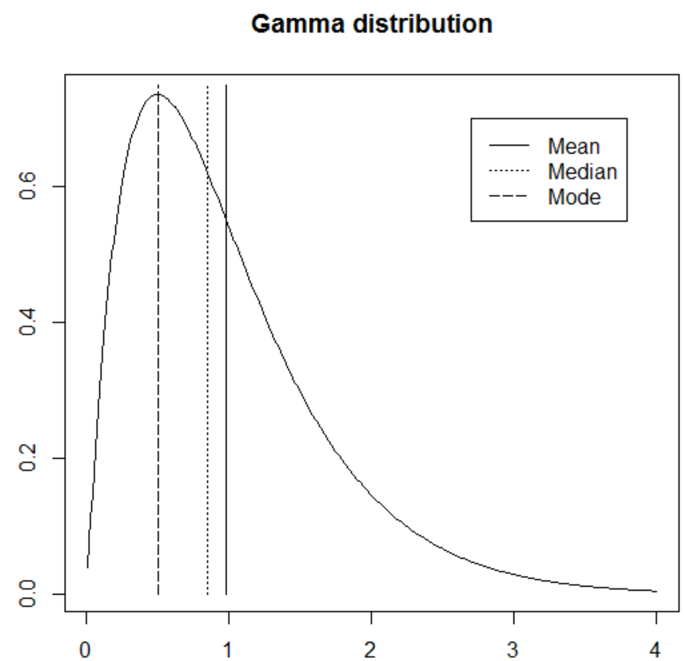
30.6	30.1	29.3	26.7	29.8
26.8	29.9	29.4	28.9	28.3
28.1	27.2	26.8	29.0	29.7
28.8	29.1	29.8	27.4	28.6
30.6	29.0	31.0	28.0	27.2
29.8	28.4	31.2	29.7	29.2

(単位kg)

Central values: mean, median, and mode

- Mean
  - Arithmetic mean, geometric mean, harmonic mean
- Median
  - The central value when the data were ordered
  - When data are even number (n = 2m), the mean of mth and m+1th values
  - Used when data are not normally distributed
- Mode
  - The most observed value

Probability density



Value of the data

Arithmetic mean

$$\bar{x} = \frac{x_1 + x_2 + \cdots + x_n}{n}$$

Geometric mean
*Used for data with outliers

$$\bar{x} = \sqrt[n]{x_1 \times x_2 \times x_3 \times \cdots \times x_n}$$

＊In the previous example, the mean was 28.9 kg

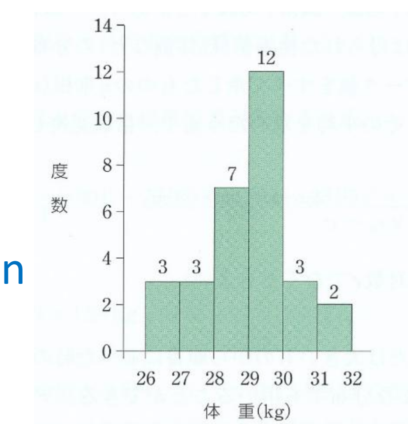


図15−1　例1のヒストグラム

There are two types of "width of a distribution"

- Variability
  - Variation in a system
  - Height is different among individuals
  - Maximum temperature today is different from the same day last year
- Uncertainty
  - Lack of knowledge
  - Degree of uncertainty, or degree of confidence on true mean

Variability

- Variability of body weight was observed as a biological system of cattle

- Variability can be expressed using range of percentile

```
summary(BW)
 Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
26.70   28.15   29.05   28.95   29.80   31.20
```

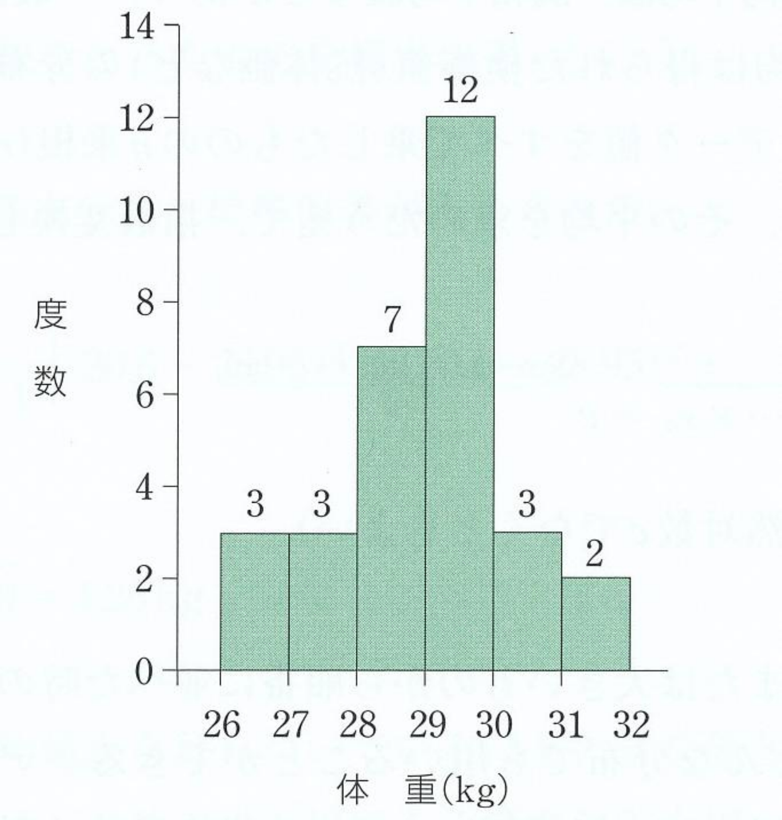


図15−1　例1のヒストグラム

＊Percentile

– When data are placed in order from the smallest to largest value, the value at x% from the smallest

Indicator of variability

- Variance (s^2)
  - Mean square of the difference between data x_i and the mean of x

$$s^2 = \frac{1}{n-1}\left\{\left(x_1 - \bar{x}\right)^2 + \left(x_2 - \bar{x}\right)^2 + \cdots + \left(x_n - \bar{x}\right)^2\right\}$$

- Standard deviation (SD, s)
  - A rout of variance (original scale)

$$s = \sqrt{s^2}$$

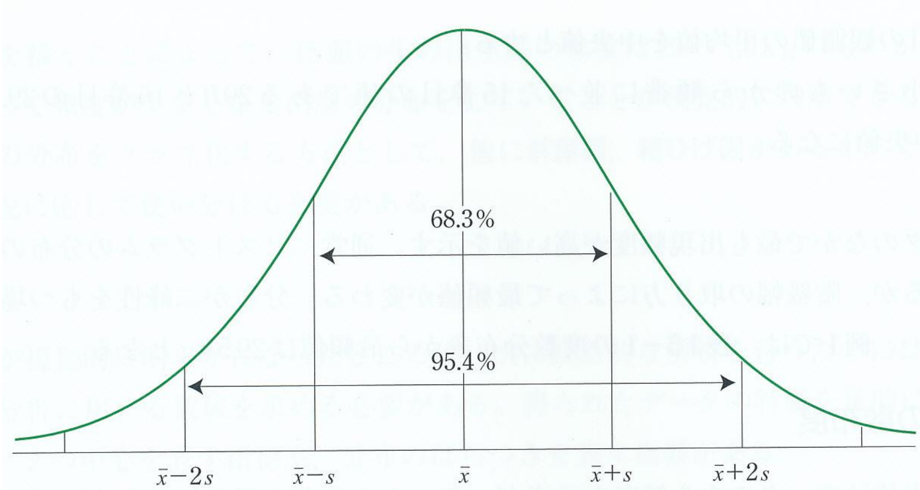
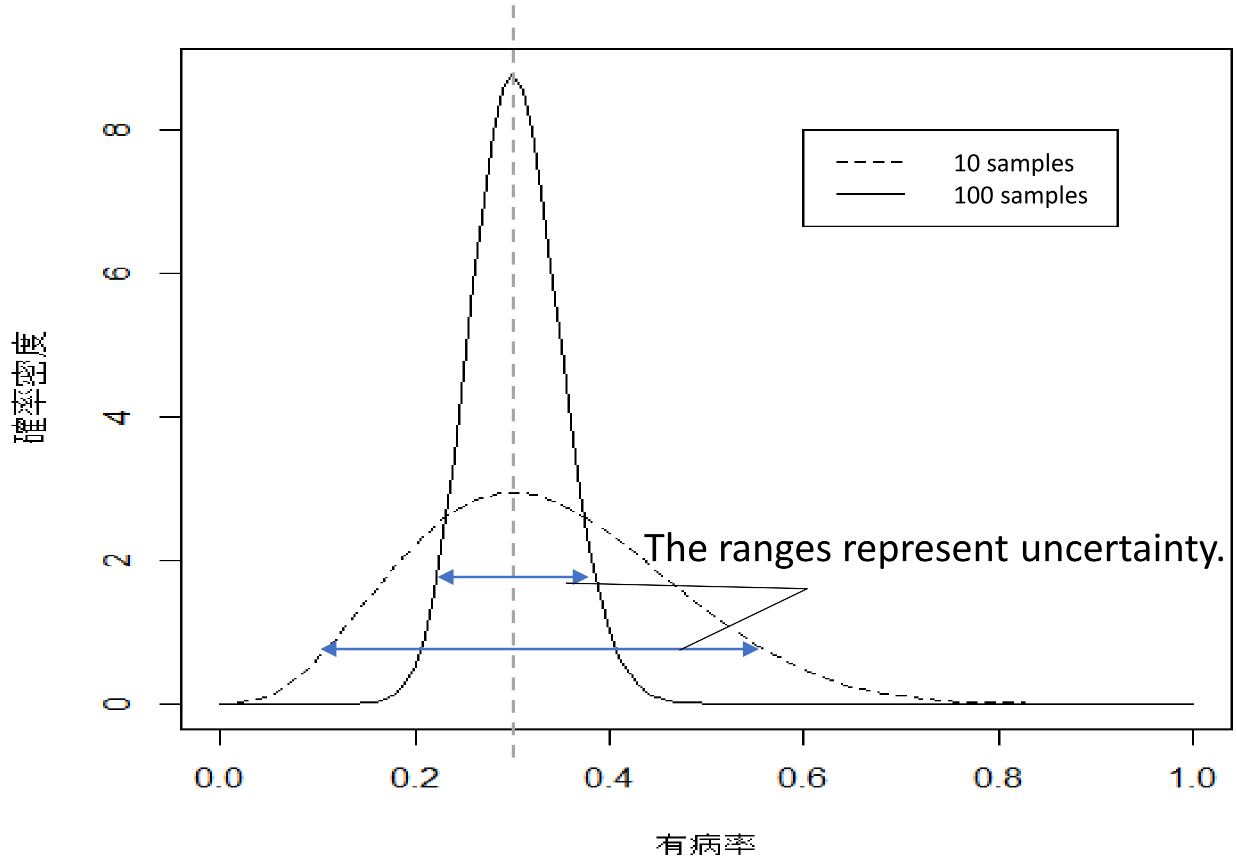


図15−2　正規分布の平均と標準偏差の関係

Uncertainty in the estimation of the mean proportion



How confidence are you when you say '30% resistant'?

- Example: resistant rate of *E. coli* for colistin
  - Out of 10 samples, 3 samples were resistant — 95%CI: 10.9 – 61.0%
  - Out of 100 samples, 30 sampled were resistant — 95%CI: 21.9 – 39.6%
  - Resistant rates are both 30%, then what is the difference?

*The exact value, 3 ÷ 10 = 0.3 is called 'a point estimate'.
On the other hand, the range that a true mean can take under probability is called interval estimate.

Estimation of the confidence interval of a proportion (A frequentist approach)

$$95\%\ \text{confidence interval} = \hat{p} \pm 1.96 \times \sqrt{\underbrace{\hat{p}(1-\hat{p})}_{\text{Variability}} / \underbrace{m}_{\text{Uncertainty}}}$$

$\hat{p}$: proportion calculated from data m: sample size

- Example: 例：40 dogs were selected from a kennel and tested for antibodies to a certain disease. 23 tested positive. Find the 95% confidence interval for the antibody positivity rate in this kennel.

```
> 23/40
[1] 0.575
> 1.96*(0.575*(1-0.575)/40)^0.5
[1] 0.1531985
> 0.575-0.153
[1] 0.422
> 0.575+0.153
[1] 0.728
```

57.5% (95%CI: 42.2% - 72.8%)

```
> qbeta(0.025,23+1,40-23+1)
[1] 0.4210961
> qbeta(0.975,23+1,40-23+1)
[1] 0.7153129
```

(Bayesian approach based on beta distribution)

57.5% (95%CI: 42.1% - 71.5%)

Estimation of 95% confidence interval of the mean of a mother population using normally distributed sample data

$$95\%\ \text{confidence interval} = \bar{x} \pm \underbrace{t_{0.05}(n-1)}_{\text{Uncertainty}} \times \underbrace{\frac{s}{\sqrt{n}}}_{\text{Variability Uncertainty}}$$

Standard error

Degree of freedom

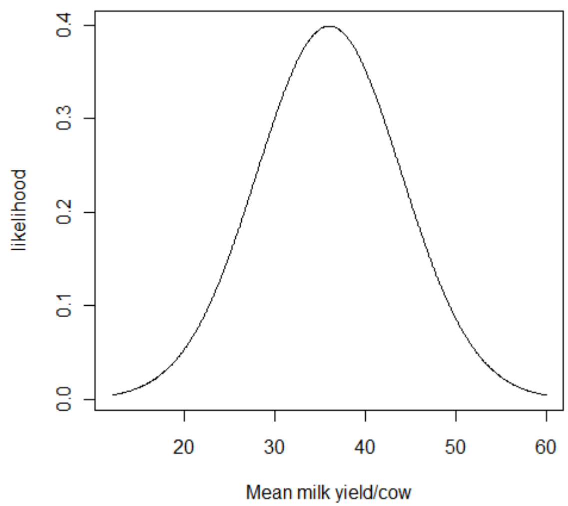
表15−2　t 分布表

自由度	両側確率 0.05	両側確率 0.01	自由度	両側確率 0.05	両側確率 0.01	自由度	両側確率 0.05	両側確率 0.01	自由度	両側確率 0.05	両側確率 0.01
1	12.706	63.66	11	2.201	3.106	21	2.080	2.831	40	2.021	2.704
2	4.303	9.925	12	2.179	3.055	22	2.074	2.819	50	2.009	2.678
3	3.182	5.841	13	2.160	3.012	23	2.069	2.807	60	2.000	2.660
4	2.776	4.604	14	2.145	2.977	24	2.064	2.797	70	1.994	2.648
5	2.571	4.032	15	2.131	2.947	25	2.060	2.787	80	1.990	2.639
6	2.447	3.707	16	2.120	2.921	26	2.056	2.779	90	1.987	2.632
7	2.365	3.499	17	2.110	2.898	27	2.052	2.771	100	1.984	2.626
8	2.306	3.355	18	2.101	2.878	28	2.048	2.763	120	1.980	2.617
9	2.262	3.250	19	2.093	2.861	29	2.045	2.756	240	1.970	2.596
10	2.228	3.169	20	2.086	2.845	30	2.042	2.750	∞	1.960	2.576

Parametric and non-parametric

Parametric

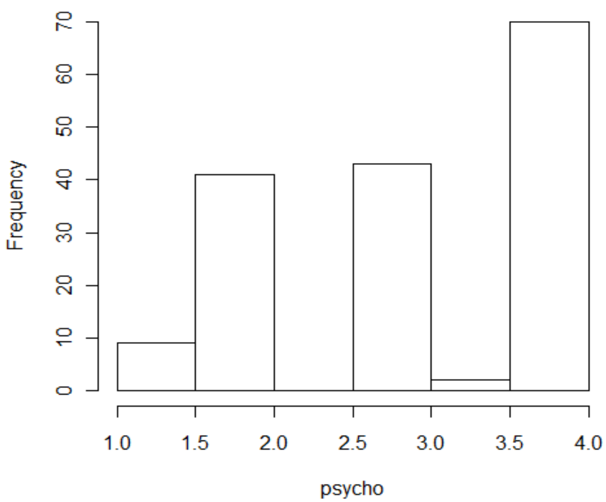
Parametric distribution is determined by parameters



Milk yield which follows normal distribution

Non-parametric

Statistics which do not use any mathematical assumption

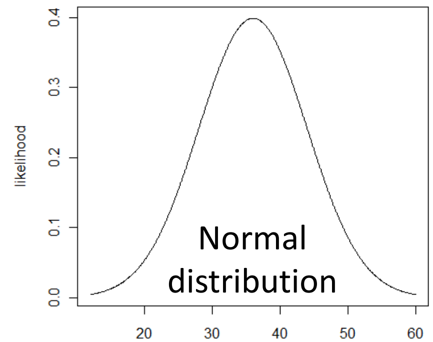


Psychological stress in foot and mouth disease control (rank)

*Parameters
Normal distribution: Mean and standard deviation
Beta distribution: Trial and success

Relationships between main distributions

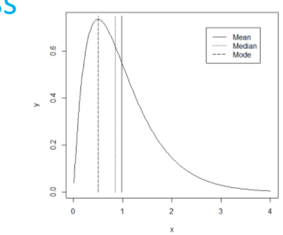
Fundamental of all statistics



Random sampling the data and take the mean
Repeating the process
(Bootstrap)

Central limit theorem

Any distribution



$$f(x) = \log x$$

Log transformation

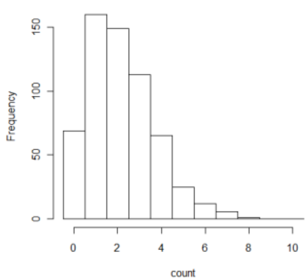
$$f(x) = \log \frac{p}{1-p}$$

Logit transformation

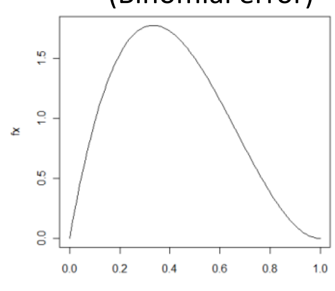
$$f(x) = \frac{1}{x}$$

Reciprocal transformation

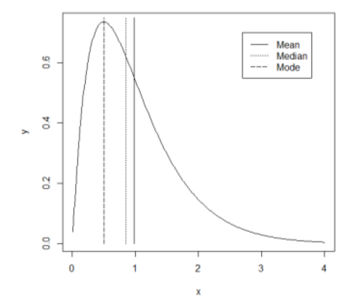
Counts (animal, human, cell)
Poisson distribution
(Poisson error)



Proportion (prevalence, disease/healthy)
Beta distribution/Binomial distribution
(Binomial error)

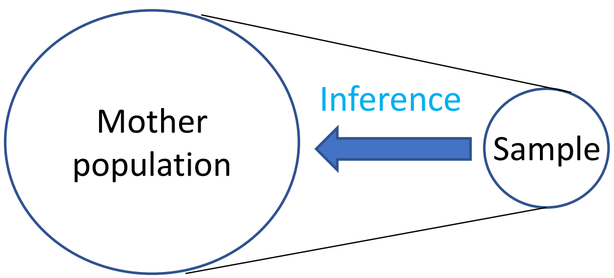


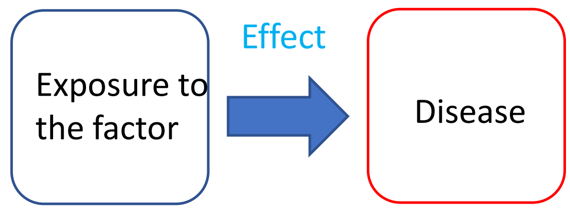
Time (time, liquid, weight)
Gamma distribution
(Gamma error)

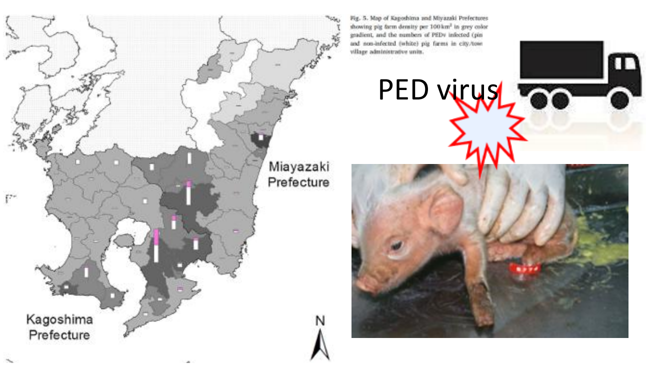


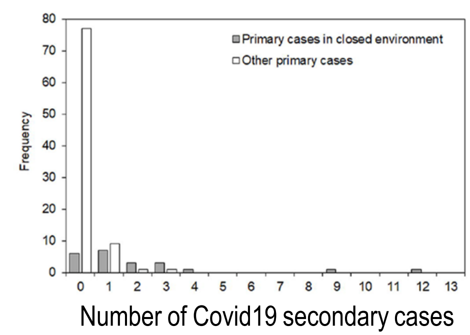
Hypothesis testing

- To probabilistically test the hypothesis that the disease occurs due to the exposure to the factor of interest in a population

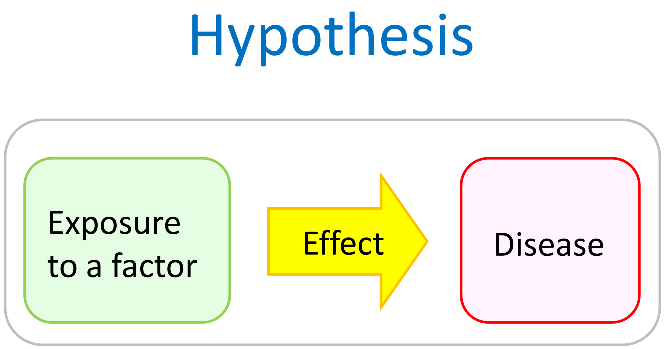


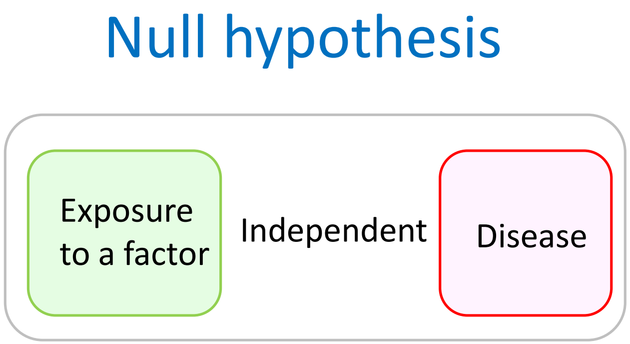






Process of hypothesis testing



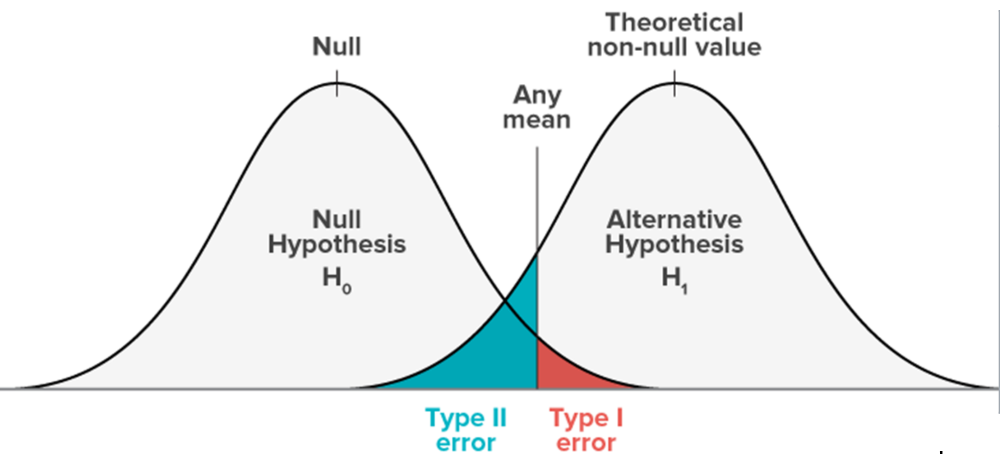


- Hypothesis
  - The proportion of multi-drug resistance *E. coli* is higher in small-scale farms than commercial large scale farms
- Develop null-hypothesis
  - The proportion of MDR *E. coli* is the same between small-scale and large-scale farms
  - (But actual calculation for p-value is the probability that large-scale farms have higher MDR rate)
- Prove that null-hypothesis is false
- Accept the hypothesis
- P-value is the probability of an event occurring under null-hypothesis

Process of hypothesis testing

- Set a hypothesis
- Set a null hypothesis (there is no effect of hypothesis)
- Prove that null-hypothesis is wrong (reject)
  - Hypothesis is correct
- Or, accept the null-hypothesis
  - Hypothesis is wrong

- Test statistics > threshold value
- At significant level 5%, $p<0.05$

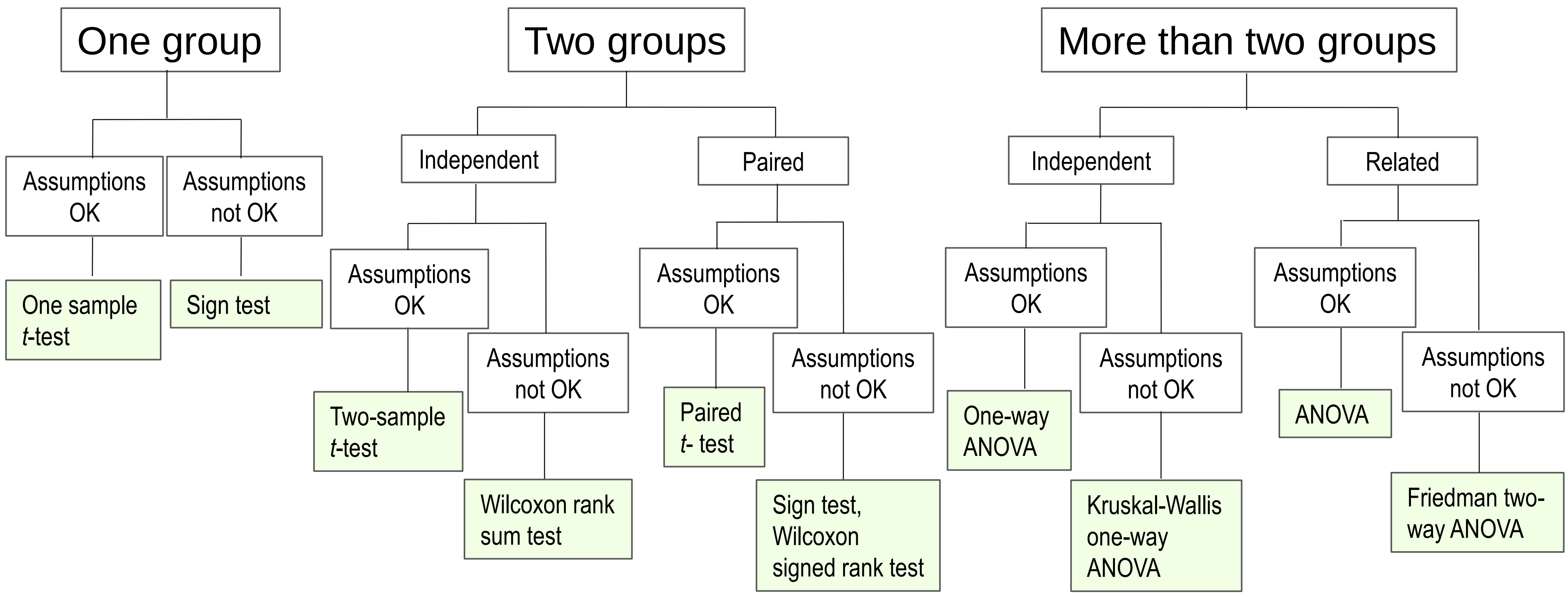


Hypothesis Null-hypothesis

		True status	
		Effect	No effect
Statistics	Effect (Reject null-hypothesis)	Correct estimate (1-β) Power	Type I error (α) *p*-value
	No effect (Accept null-hypothesis)	Type II error (β)	Correct estimate (1-α)

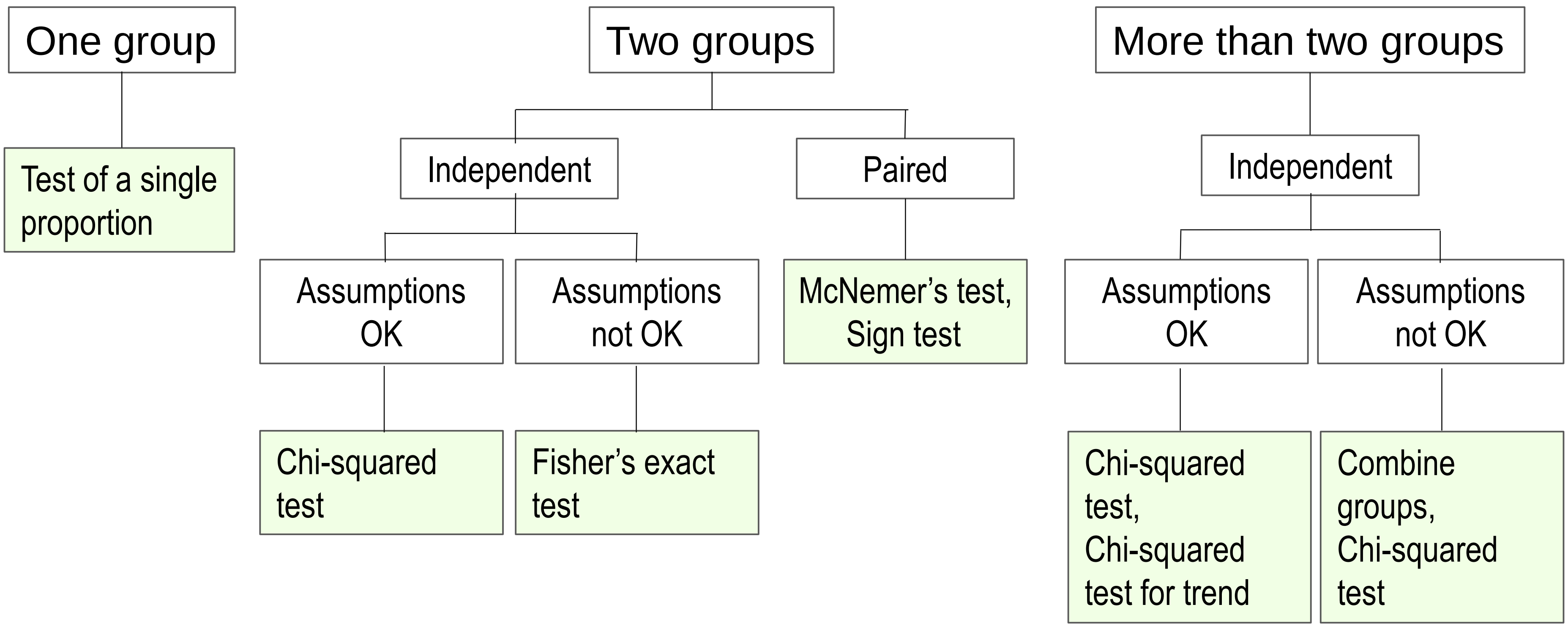
＊ ***p*-value** is a probability that null-hypothesis is observed when null-hypothesis is true

Flow chart for the comparison of groups in continuous/count/rank variables



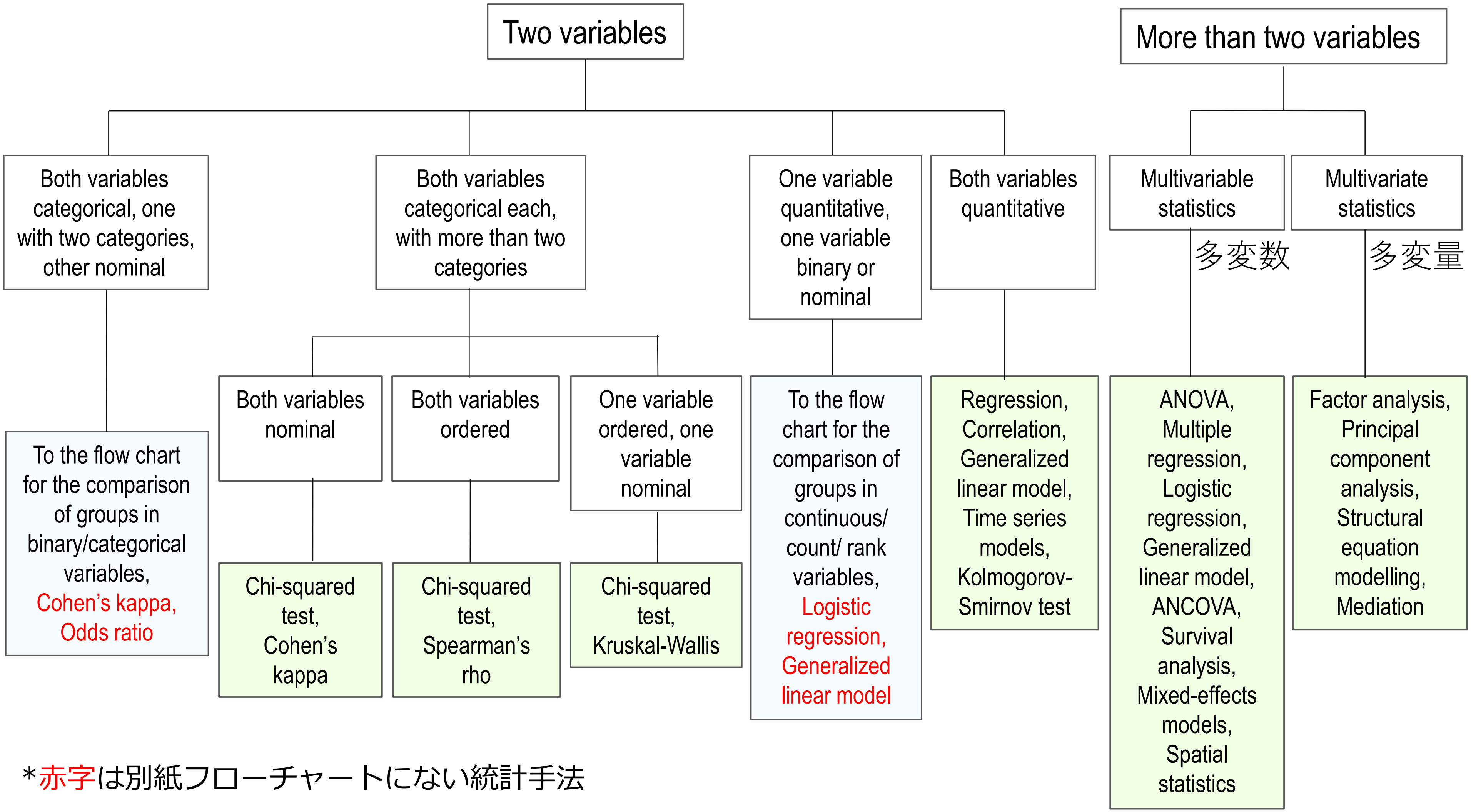
*Assumptions: data follow Normal distribution and variance is not significantly different when comparing more than or equal to two variables.

Flow chart for the comparison of groups in binary/ categorical variables



*Assumptions: at least one cell include expected frequency smaller than five.

Flow chart for the analyses of the relationships between variables



*赤字は別紙フローチャートにない統計手法

Any questions?