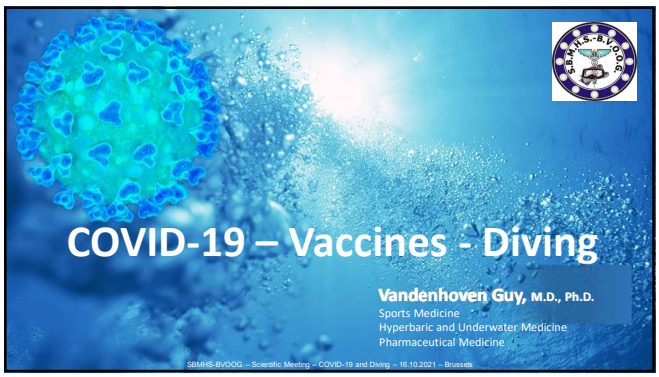

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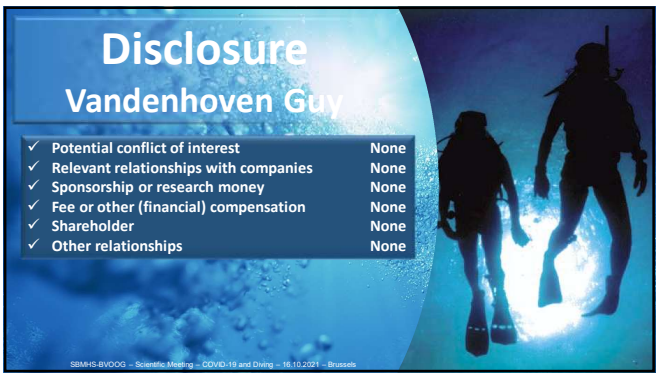

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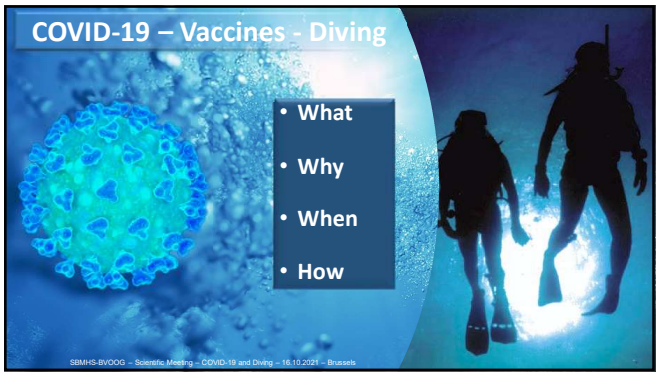

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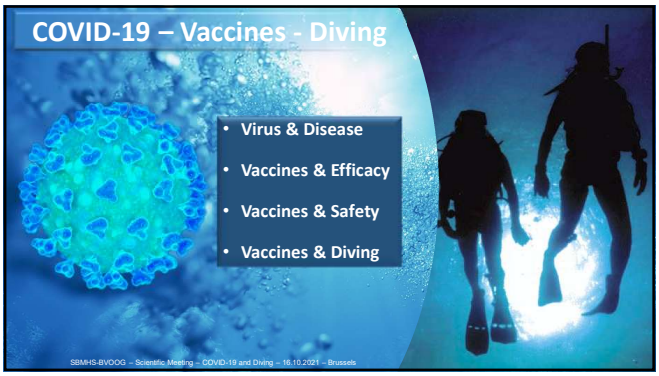

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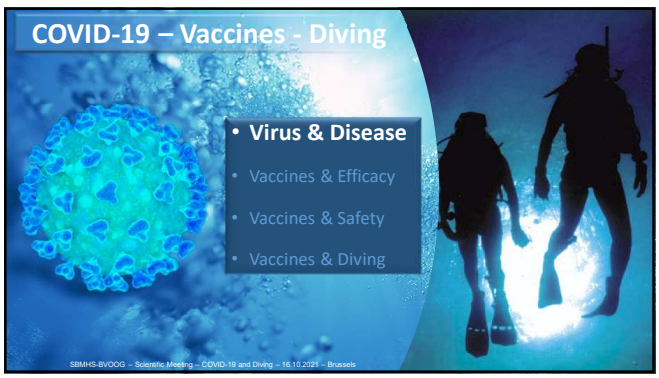

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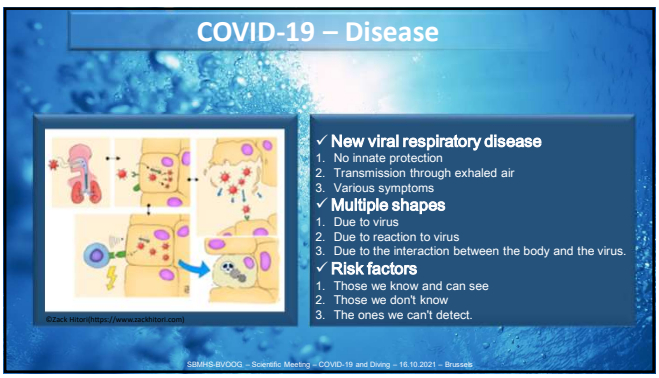

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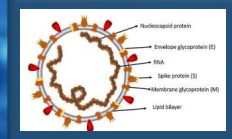
SARS-CoV-2 - Virus



- ✓ RNA encapsulated virus
- ✓ Binding to cells
  - Via Protein S (spike)
  - In the respiratory tract (from the nose / sinuses to the lungs)
- ✓ Injection of genetic material (RNA) into the cell
- ✓ Using cell mechanics to replicate

7

COVID-19 - Complications

- ✓ Medium and long-term sequelae
- ✓ Risk of hospitalisation
  - Especially in certain groups but not only
  - Consequences of hospitalization (nosocomial infection, thrombosis, …)
  - Post-intensive care syndrom
- ✓ Risk of death
  - Very low amongst young people, this is clearly not the argument
- ✓ Psycho social impact
  - Isolement
  - School dropout/impact on education
  - Anguish (if I infect a loved one and he or she dies ?)

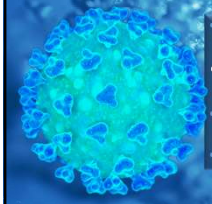
8

Long COVID-19

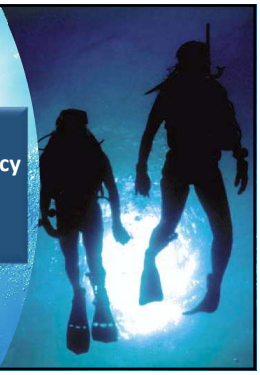
- ✓ Persistence of some symptoms for more than 8 weeks
  - Sometimes more than 6 months
  - Anosmia
  - Physical deconditioning
  - Cognitive impairment (head in the fog)
- ✓ An estimated 10 to 25 % of non hospitalized people
- ✓ Up to 60 % of patients in hospital
- ✓ Positive impact of vaccination on this syndrome
- ✓ Prevention through vaccination
- ✓ Risk factor for other pathologies
  - Depression
  - Risk associated with a sedentary lifestyle / lack of activity

9

COVID-19 – Vaccines - Diving



- Virus & Disease
- **Vaccines & Efficacy**
- Vaccines & Safety
- Vaccines & Diving



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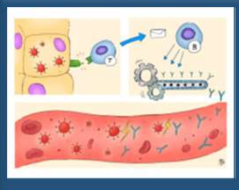
How do vaccines work ?



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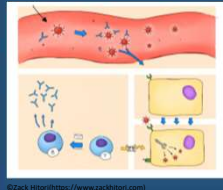
- ✓ We don't do better than immunity
- ✓ Use immunity as in the case of the disease but with less inconvenience
- ✓ The processus to do recognize a part of the body of the virus we want to fight
- ✓ More than 100 years of hindsigfht

11

Actors of immunity



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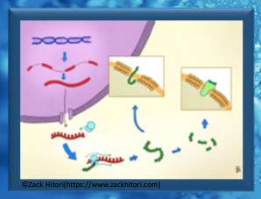
- ✓ **B lymphocyte**: long-term immunity, entrained in the lymph nodes following the local immune reaction.
- ✓ **T lymphocyte**: recognition of pathogens, initiation of the reaction immune and cell destruction infected (NK)
- ✓ **Antibodies**: produced by B lymphocytes, recognizes the pathogen and allows its destruction by other immune cells (PMNN and macrophage)

Immunity is not an on / off system, but a machine which improves itself.

12

Cellular biology



1. Transcription of DNA into pre-RNA messenger
2. Modification of this pre-RNA into RNA messenger (mRNA)
3. Output of mRNA from the nucleus via nuclear pores (one way)
4. Recruitment of ribosomes that translate mRNA into protein
5. A 1st part of the proteins go to the cell surface
6. A 2nd part is cut into segments presented to the immune system

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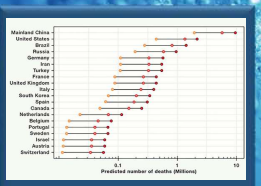
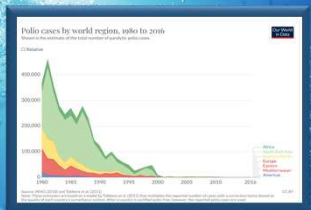
The most effective solution against viruses

« Immunization is one of the most effective and cost-effective public health interventions » WHO



Mortality without vaccine intervention



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Vaccine Platform Refresher (1)

Platform	About	Licensed products
Inactivated	Inactivated vaccines consist of the whole virus, which has been killed with heat or chemicals so that it can't cause illness. In general, inactivated virus vaccines do not provide as strong of an immune response as live attenuated vaccines, so additional doses may be needed.	Polio
Live attenuated	Live attenuated vaccines are made up of whole viruses that have been weakened in a lab (usually through culturing). They tend to elicit a stronger immune response than inactivated vaccines.	MMR Varicella TB
Subunit	Subunit vaccines introduce a fragment or portion of the virus into the body. This fragment is enough to be recognized by the immune response and stimulate immunity.	Pertussis HPV Hep. B
Viral vector	Viral vector vaccines insert a gene for a viral protein into another, harmless virus (replicating or non-replicating). This harmless virus then delivers the viral protein to the vaccine recipient, which triggers an immune response. • **Replicating viral vectors** are able to produce copies of the viral protein, potentially triggering an enhanced immune response.	Ebola Veterinary vaccines
mRNA	RNA vaccines work by introducing an mRNA sequence (the molecule that tells cells what to build) coded for a disease-specific antigen. Once this antigen is reproduced within the body, it is recognized and triggers an immune response.	None
DNA	DNA-based vaccines work by inserting synthetic DNA of viral gene(s) into small DNA molecules called plasmids. Cells take in the DNA plasmids and follow their instructions to build viral proteins, which are recognized by the immune system, and prepare it to respond to disease exposure.	None

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Vaccine Platform Refresher (2)

DNA-based vaccines work by inserting synthetic DNA of viral gene(s) into small DNA molecules (called plasmids). Cells take in the DNA plasmids and follow their instructions to build viral proteins, which are recognized by the immune system, and prepare it to respond to disease exposure

SANOFI INOVIO

Viral vector vaccines insert a gene for a viral protein into another, harmless virus (replicating or non-replicating), which delivers the viral protein to the vaccine recipient, triggering an immune response.

AstraZeneca Johnson & Johnson MERCK CanSinoBIO

RNA vaccines introduce an mRNA sequence coded for a disease-specific antigen. Once this antigen is reproduced within the body, it is recognized and triggers an immune response

Pfizer moderna CUREVAC

Subunit vaccines introduce a fragment of the virus into the body. This fragment is enough to be recognized by the immune response and stimulate immunity.

NOVAVAX Clover

Inactivated vaccines consist of the whole virus, which has been killed with heat or chemicals so it can't cause illness.

sinovac

Live attenuated vaccines are made up of whole viruses that have weakened in a lab. They tend to elicit a stronger immune response than inactivated vaccines.

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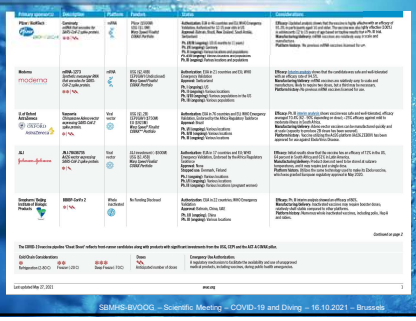
COVID-19 Vaccin pipeline (1)



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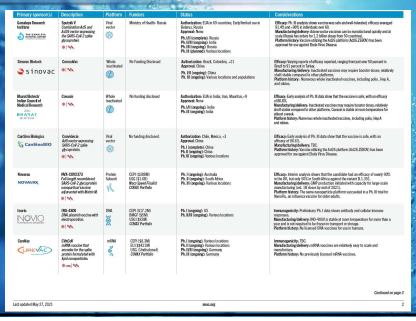
COVID-19 Vaccin pipeline (2)



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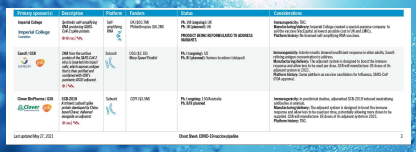
COVID-19 Vaccin pipeline (3)



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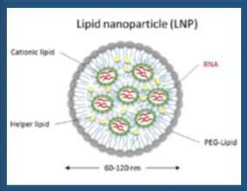
COVID-19 – RNA Vaccines



- Lipides
  - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (**ALC-0315**)
  - 2-[(*polyethyleneglycol*)-2000]-N,N-ditetradecylacetamide(**ALC-0159**)
  - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
  - Cholesterol
- **Potassium chloride**
- **Potassium dihydrogenphosphate**
- **Sodium chloride**
- **Disodiumphosphate dihydrate**
- **Sucrose**
- **Water for injections**

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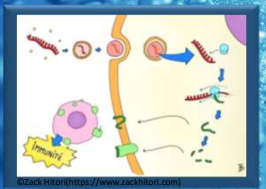
COVID-19 – RNA Vaccines



1. Lipids encompass mRNA
2. Presentation of the "bag" to the cell
3. Entry into the cell (endocytosis)
4. Release of RNA into the cytoplasm
5. mRNA recruits ribosomes
6. Synthesis of protein S
7. Some of it goes to the surface of the cell
8. The other is cut into segments presented in immune system
9. These are recognized as foreign to the body and cause an immune response.
10. Protein on the surface helps stimulate immune reaction that creates immunity.

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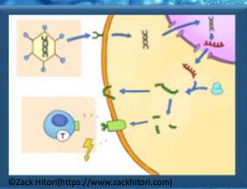
COVID-19 – Viral Vector Vaccines



1. Injection of the vaccine containing the vector viral
2. Binding of the vector with the target cell
3. Injection of genetic material ("Infection")
4. Use of cellular machinery to synthesize protein S
5. Expression at the membrane for a part of the proteins produced
6. Cutting and presentation to the system immune for a small part
7. Recognition of a protein foreign by the immune system and triggering of the immune reaction
8. Development of immunity

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Research & Development Timelines

- ✓ As part of development of vaccine, **all control steps** were **followed**
- ✓ **Lack** of **funding** and **recruitment problem**
- ✓ Theoretical, **in vitro development** already been carried out **before the start of the pandemic** for other diseases (Ebola in particular)
- ✓ What allowed the **acceleration of the process**:
  - **Overlapping clinical phases**
  - **Continuous assessment of dossier** by **EMA** and **priority dossier**
  - **Production** started **before marketing authorization**

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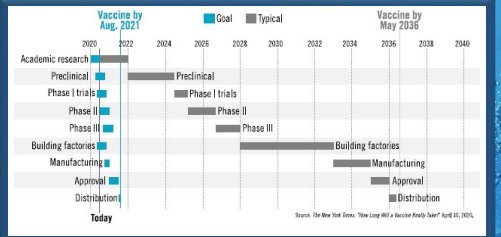
COVID-19 – Vaccines – R & D



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COVID-19 Vaccine R & D Timelines

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Strategies to shorten COVID-19 vaccine R & D timelines

- Multiple vaccine approaches
- Concurrent testing
- Rapid data sharing
- Emergency regulatory approval
- New approaches to funding and research collaboration
- Early manufacturing scale-up
- A global sense of urgency

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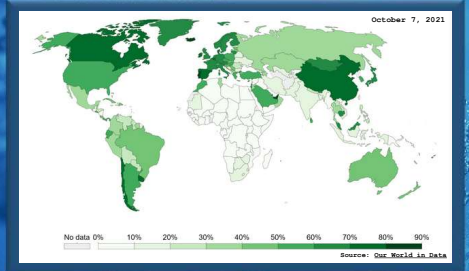
COVID-19 - Share of Population Fully Vaccinated



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COVID-19 Vaccine efficacy

30-day cumulative incidence of COVID-19 cases (symptomatic & asymptomatic) (11/08 to 11/09/2021)

Age group	Not fully vaccinated Cases per 100k unvaccinated population	Fully vaccinated Cases per 100k vaccinated population	Relative risk reduction, % (2SD)
00-17	880	104	88.2 (86-90)
18-24	2054	199	90.3 (89-92)
25-44	1945	289	85.1 (83-87)
45-64	1240	209	83.1 (80-85)
65-79	472	130	72.6 (67-77)
80+	272	157	42.5 (30-53)

28

COVID-19 Vaccine efficacy

30-day cumulative incidence of COVID-19 hospitalizations (COVID symptoms) (11/08 to 11/09/2021)

Age group	Not fully vaccinated Hospitalizations per 100k unvaccinated population	Fully vaccinated Hospitalizations per 100k vaccinated population	Relative risk reduction, % (2 SD)
00-17	N/A	N/A	N/A
18-24	5.4	0	100 (100-100)
25-44	12.9	0.14	98.9 (97-100)
45-64	33.3	1.0	96.9 (94-98)
65-79	40.4	3.3	92.0 (87-95)
80+	37.7	8.7	77.0 (42-89)

NB This hospital register is not exhaustive and does not contain all hospitalized COVID-19 patients. On top of this, regional differences in registration of hospitalized patients may skew the results.

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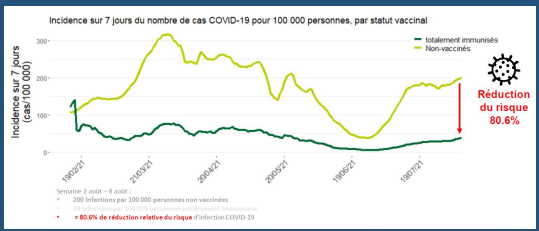
COVID-19 Vaccine efficacy

Infections less frequent in vaccinated persons



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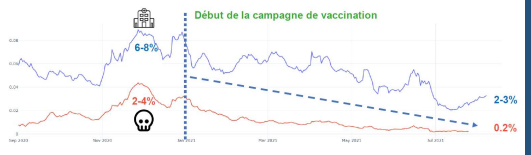
COVID-19 Vaccine efficacy

Risk of hospitalisation and death



Le nombre d'**hospitalisations par infection** diminue (**7 sur 100** à **2.5 sur 100**)
Le nombre de **décès par infection** diminue (**3 sur 100** à **0.2 sur 1000**)

(Ce graphique tient compte de la différence de temps entre l'infection et l'hospitalisation ou le décès)

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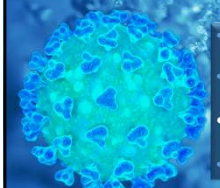
COVID-19 – Vaccines - Diving



- Virus & Disease
- Vaccines & Efficacy
- **Vaccines & Safety**
- Vaccines & Diving

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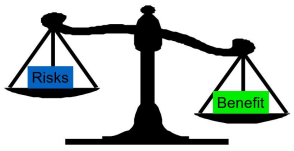
COVID-19 – Vaccines & Safety

In order to market a drug benefit must outweigh risks

Self evident ?



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COVID-19 – Vaccines & Safety

Efficacy ("benefit") & Safety ("risks")

The fundamental difference

Efficacy
Focus on one or a few well defined symptoms and/or diagnoses

Safety
Everything Else !

There are 4000 diagnoses and 50000 symptoms to choose from !

We decide what we mean by efficacy !

We can never decide what will happen !

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COVID-19 – Vaccines & Safety

Adverse Drug Reaction (ADR) ("side effect")

An adverse drug *reaction* is an adverse event considered to be causally related to the product.

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COVID-19 – Vaccines – Adverse Drug Reactons

- ✓ **Related to the immune reaction**
  - Shows that the vaccine is playing its role
  - Local (pain, redness, swelling)
  - General (fatigue, flu syndrome, fever or febrile state)
- ✓ **Allergic reaction**
  - Anaphylactic shock, hence the monitoring after the reaction
  - Mild allergic reactions (hives, swelling, etc.)
- ✓ **Vaccine induced Immune Thrombotic Thrombocytopenia**
  - Concerns viral vector vaccines
  - Very rare
- ✓ **Heart problem (myocarditis, pericarditis)**
  - Very rare (around ten per million vaccinations)
  - Complete recovery in the majority of cases

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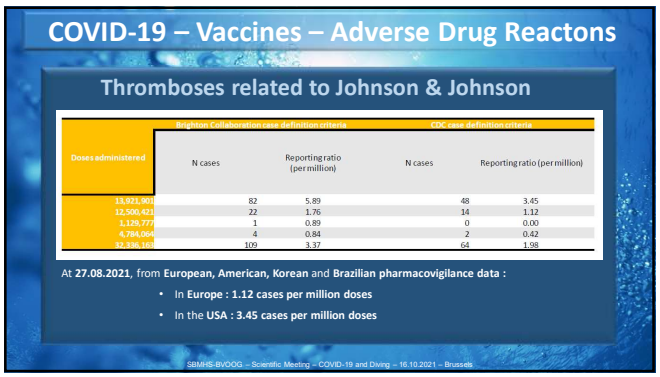

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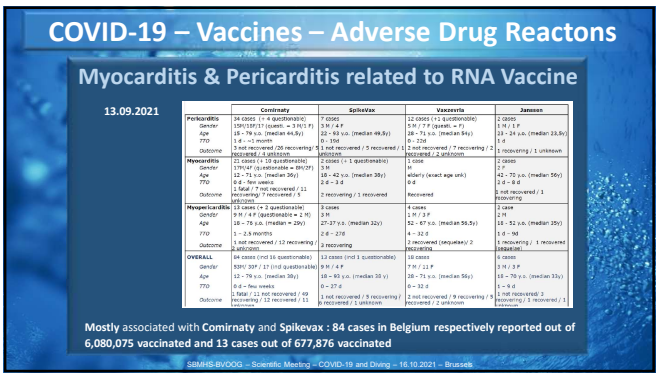

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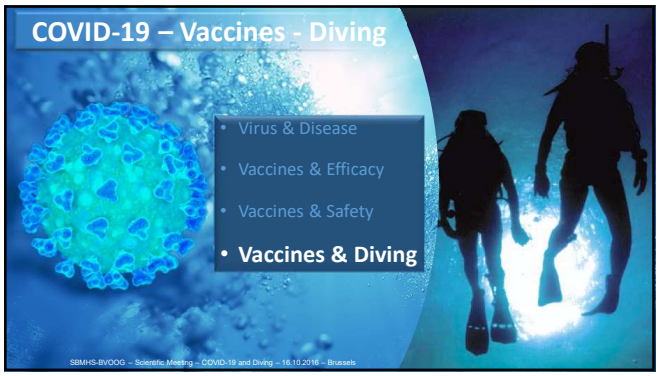

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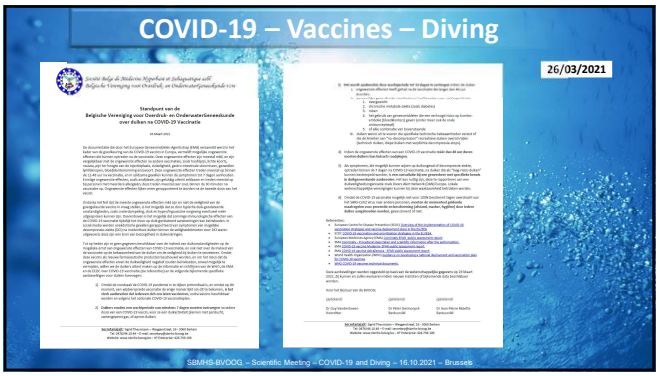

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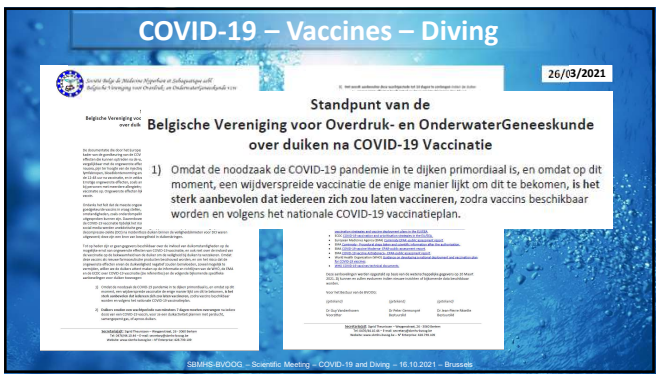

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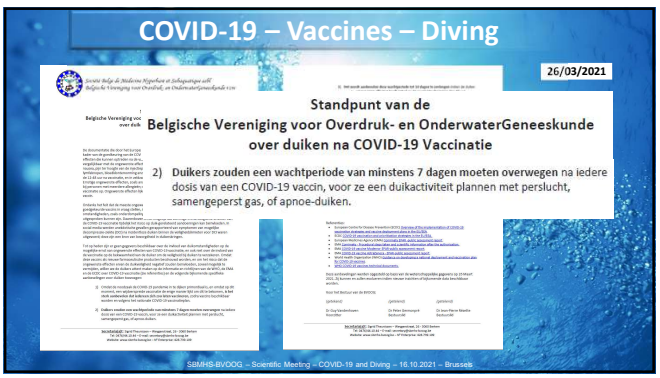

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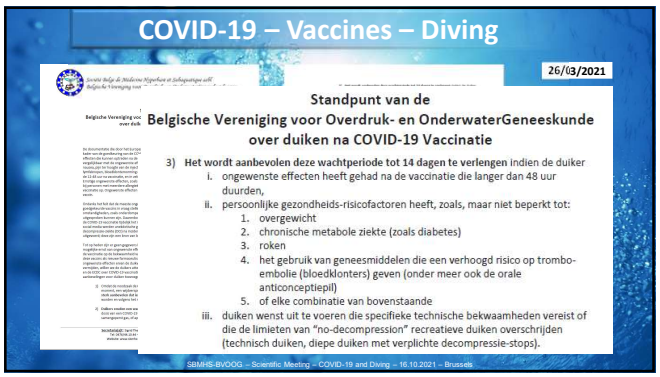

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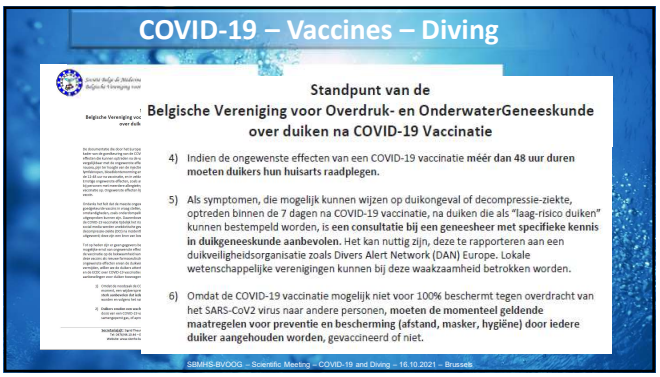

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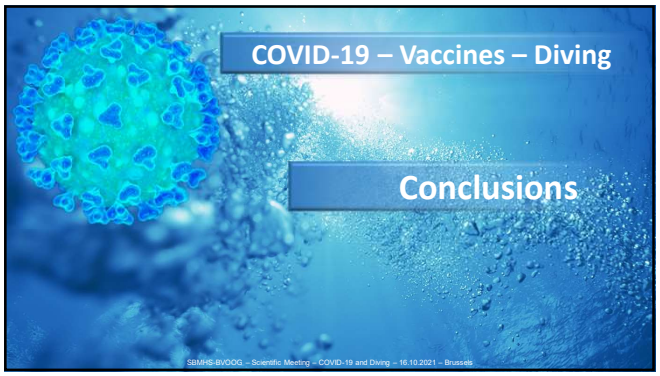

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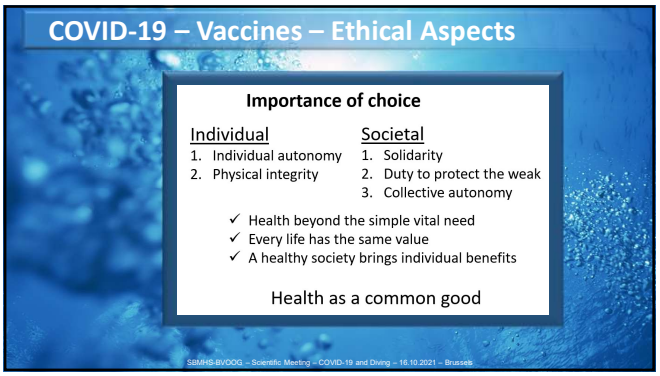

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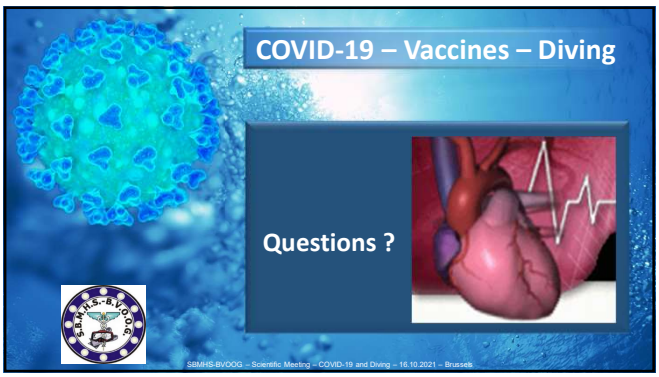

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