April 16, 2016
Edmonton, AB

Mr. Shawn Buckley
Via Email

Re. Death of Ezekiel Stephan (OCME file 1018-7289)

Mr. Buckley,

The present letter is to convey my expert opinion on the death of Ezekiel Stephan. To prepare this opinion, I had access to the following material:

- The medical examiner's file;
- A report from a CT-scan of the head (3 pages);
- The medical file of Ezekiel Stephan as originally disclosed to the Defence (page numbers are Defence file page numbers);
- The transcripts from the two days of testimony of Dr. Adeagbo at the preliminary inquiry (98 pages and 64 pages) – I was instructed not to refer to this document in the present report;
- The transcript from the testimony of Mr. Cherniawsky at the preliminary inquiry (22 pages) – I was instructed not to refer to this document in the present report;
- Two 911 calls from March 13, 2012 (3:43 minutes and 11:59 minutes);
- Report from the Emergency Medical Services (5 pages);
- 16 autopsy pictures;
- 13 microscopic slides of all major organs;
- The transcript from the testimony of Dr. Adeabgo at the trial (193 pages).

Ezekiel Stephan (18 months) suffered from croup and meningitis-like symptoms. He went into respiratory arrest (March 13) and there were issues during the paramedic interventions that prolonged the period of respiratory arrest by approximately 8 minutes. On arrival at the hospital, Ezekiel had already suffered severe hypoxic and anoxic brain injury. Despite medical intervention, he was declared brain dead (March 16), and life support was ceased after 5 days (March 18). The autopsy was performed on March 19, and revealed the presence of meningitis and right pleural empyema.

Four aspects of this summary are of particular importance:

a) Croup;
b) Meningitis;
c) Medical misadventure during the paramedic intervention;
d) Right pleural empyema.

1. Most likely infectious agent

1.1 Croup, and most likely infectious agent

Ezekiel presented with intermittent symptoms of croup in the two weeks prior to the respiratory arrest of March 13. Furthermore, his respiration, as can be heard on the first 911 call of March 13, is characteristic of airway obstruction, which could be suggestive of croup (laryngotracheobronchitis).

The croup is usually caused by viruses, though it can sometimes be caused by bacteria. Table 1 presents the usual infectious agents in croup (adapted from Zoorob et al, 2011)[1].

Table 1 – Infectious agents in croup

Type	Infectious Agents
Virus - Frequent	Parainfluenza virus
Virus – Occasional to frequent	Enterovirus, Rhinovirus, Bocavirus, Influenza A and B, Respiratory Syncytial Virus
Virus - Occasional	Adenovirus
Virus - Rare	Measles
Bacteria	*Staphylococcus aureus, Haemophilus influenzae, Group A. streptococcus*

At autopsy, the report from a nasopharyngeal wash/swab was positive for "Enterovirus or Rhinovirus" (see p. 13 of the medical examiner's file). In this particular case, considering this positive result, the most likely infectious agent to explain the croup is enterovirus or rhinovirus.

Of note, Dr. Adeagbo was asked "*when you did the autopsy, you didn't see evidence of croup; is that fair to say?"* He answered (p. 80): "*I did not see evidence of croup."* However, he failed to say that autopsy findings in viral croup are usually indistinguishable from the observations that are expected from mechanical ventilation with intubation. Therefore, the absence of specific autopsy findings is of no importance here and does not exclude a viral croup.

[1] Zoorob R, Sidani M, Murray J (2011). Croup: an overview. Am Fam Physician. 83(9):1067-73.

Furthermore, it is important to insist that croup is a clinical diagnosis, not a diagnosis established at autopsy:

> *"Croup is primarily a clinical diagnosis, with the diagnostic clues based on presenting history and physical examination findings."*[2]

1.2 Meningitis, and most likely infectious agent

Ezekiel apparently presented with symptoms of meningitis, diagnosis that was later confirmed at autopsy: a film of pus covers some parts of the brain (presence of a fibrinopurulent exudate in the subarachnoid space).

When a child presents with symptoms of meningitis, the infectious agent is more likely to be viral (95%) than bacterial (only 5%).[3]

Viral meningitis is caused most often by enteroviruses, in 85 to 95% of cases (Rotbart 2000).[4]

Bacterial meningitis in children are most often caused by *Neisseria meningitidis* (50-60%), *Streptococcus pneumoniae* (25-30%), *Haemophilus influenzae* (<5%), *Streptococcus* group A, B and D (2-4%), *Staphylococcus aureus* (1-2%), *Listeria monocytogenes* (1-2%), and Gram-negative bacilli (1-2%).[5]

In this particular case, a lumbar puncture was not performed at the hospital (see p. 396 of the medical file). Therefore, we don't know what infectious agent was present in the cerebrospinal fluid. At autopsy, no bacterial growth was observed on the cerebrospinal fluid culture (p. 12 of the medical examiner's file).

1.2.1 A predominance of neutrophils would not have excluded a viral meningitis

Dr. Adeagbo described the predominance of neutrophils at autopsy in the pus covering the brain. Based on this predominance of neutrophils, Dr. Adeagbo excluded a virus as the infectious agent (p. 66 and 67 of the trial transcript). He was asked: *"Did a virus cause Ezekiel to die?"* He answered: *"No." He was then asked: "Why do you say that?"* He answered: *"I say that because all the findings, they are not -- the autopsy findings are more in -- more consistent with a bacteria infection (…) the histologic assessment of the cells that were involved in the reaction also support a bacteria rather than a virus."* (note: he also gave another reason, the presence of a few Gram-negative bacilli, which will be discussed later)

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[2] http://emedicine.medscape.com/article/962972-workup

[3] See online Neuropathology by Agamanolis: http://neuropathology-web.org/chapter5/chapter5aSuppurative.html

[4] Rotbart HA (2000). Viral meningitis. Semin Neurol. 20(3):277-92.

[5] In Practical surgical neuropathology: A diagnostic approach, by Perry and Brat. Available online: https://goo.gl/70TAEN

Purulent meningitis with abundant neutrophils is usually characteristic of bacterial meningitis. However, it is important to note that there are multiple exceptions, and that the observations in viral and bacterial meningitis can overlap.

In Practical Surgical Neuropathology, it is written:[6]

> *"At the other end of the spectrum, some cases of viral meningitis in their acute phases manifest with a CSF profile that includes considerable amount of PMNs (…) and in these instances, neutrophils are also found in the meninges by the pathologist."* (note: CSF: cerebrospinal fluid; PMN: polymorphonuclears, which refer here to the neutrophils)

The fact that viral meningitis can present with abundant neutrophils is particularly well known with enteroviruses.

Tan et al (2016)[7] studied 206 children to see if the cerebrospinal fluid cell count would be discriminatory or otherwise for enteroviral meningitis in infants and young children. They wrote that the cerebrospinal fluid in enteroviral meningitis can sometimes cause a pleocytosis (i.e. an increase in white cells) *"with some pleocytosis levels suggestive of bacterial meningitis."* They added: *"it might be challenging to differentiate between bacterial and EV meningitis based on initial CSF analysis."* (EV: enteroviral).

Following an enterovirus epidemic outbreak in Finland, Osterback et al (2015)[8] found that the number of white cells and the proportion of lymphocytes versus neutrophils were variable between cases. In some patients, a predominance of neutrophils up to 96% was observed.

In Wolfaardt et al (2014)[9], they studied a cluster of enteroviral meningitis in children in South Africa and found that in children with pleocytosis, there was a predominance of neutrophils in 60% (12 out of 20 patients). This overlap between the findings in enterovirus and bacterial meningitis for white cells counts and neutrophils is also emphasized in Hysinger et al (2012).[10]

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[6] In Practical surgical neuropathology: A diagnostic approach, by Perry and Brat. Available online: https://goo.gl/wn8qjq

[7] Tan NW, Lee EY, Khoo GM, Tee NW, Krishnamoorthy S, Choong CT (2016) Cerebrospinal fluid white cell count: discriminatory or otherwise for enteroviral meningitis in infants and young children? J Neurovirol. 22(2):213-7.

[8] Österback R, Kalliokoski T, Lähdesmäki T, Peltola V, Ruuskanen O, Waris M (2015). Echovirus 30 meningitis epidemic followed by an outbreak-specific RT-qPCR. J Clin Virol. 69:7-11

[9] Wolfaardt M, Büchner A, Myburgh M, Avenant T, du Plessis NM, Taylor MB (2014). Molecular characterisation of enteroviruses and clinical findings from a cluster of paediatric viral meningitis cases in Tshwane, South Africa 2010-2011. J Clin Virol. 61(3):400-5.

[10] Hysinger EB, Mainthia R, Fleming A (2012). Enterovirus meningitis with marked pleocytosis. Hosp Pediatr. 2(3):173-6.

Therefore it is not possible to exclude viral meningitis based on the neutrophils predominance.

1.2.2 There is no predominance of neutrophils in the fibrinopurulent exudate in the subarachnoid space

In the present case, a review of the microscopic slides of the fibrinopurulent exudate in the subarachnoid space does not reveal a neutrophil predominance. The fibrinopurulent exudate is mainly composed of dead cells and debris, with some few remaining identifiable lymphocytes (including plasmocytes), monocytes, and neutrophils. A careful examination of the leukocytes population is more in favor of a predominance of lymphocytes and monocytes than of a predominance of neutrophils.

The microscopic examination of the fibrinopurulent exudate is not consistent with the statement of Dr. Adeagbo that the infectious agent must be a bacteria. On balance of probability, considering all the elements known in this case, a virus is a far more likely infectious agent (most likely an enterovirus).

1.3 There is no valid scientific evidence to support *Haemophilus influenzae* as the infectious agent in this case

It is worth stating again that in this case, a lumbar puncture was not performed at the hospital. At autopsy, no bacterial growth was found on the cerebrospinal fluid culture, on the blood culture or on the cultures from the lungs. A Gram staining demonstrated a few Gram-negative bacilli in the right lung and scant Gram-negative bacilli in the cerebrospinal fluid. Therefore, we don't know what infectious agent was present in the cerebrospinal fluid and the lungs. At autopsy, the report from a nasopharyngeal wash/swab was positive for "Enterovirus or Rhinovirus".

Despite these facts, Dr. Adeagbo stated (p. 35): "Based on the DNA we found out that that gram-negative bacilli was a Haemophilus influenzae." There are multiple issues with this statement, and with further statements he made on the same topic.

1.3.1 *Haemophilus influenzae* is a Gram-negative coccobacillus

Earlier in his testimony (p. 33), Dr. Adeagbo had explained what a bacilli is: *"we have a gram-negative organisms, and the shape is described as "bacilli". Bacilli actually means "rod". Rod is -- usually there are -- there's two type of shape, a circular shape called the "cocci" or "coccus" are the rod shape called the "bacilli"."*

However, *Haemophilus influenza* is a Gram-negative coccobacillus, which means that this bacteria has an intermediate shape between cocci (spherical bacteria) and bacilli (rod-shaped bacteria).

> *"Haemophilus species are Gram-negative coccobacilli"* (Medical Microbiology, 4th edition)[11]
>
> *"Haemophilus: They are Gram-negative, non-motile coccobacilli"* (A short textbook of microbiology)[12]

1.3.2 16S rRNA gene sequence analysis is not prime for clinical use

From the results of a test called 16S rRNA gene sequence analysis, Dr. Adeagbo concluded: *"Based on the DNA we found out that that gram-negative bacilli was a Haemophilus influenzae."* (p. 35)

Dr. Adeagbo acknowledged that the DNA sequence coding for 16s rRNA is still a research tool (p. 35): *"I decided to speak with the microbiology expert on this (…) we have this research technology that we are working on".* This can also be seen from an extract of the preliminary inquiry, cited at trial (p. 166): "*therefore, a non-clinical research methodody (sic) -- methodology."* The same terminology is used in his autopsy report form: *"Given that the microbiological culture did not produce positive culture report (…) therefore a non-clinical research methodology to detect microorganisms DNA coding was utilized and this resulted in identification of Haemophilus Influenzae in the cerebrospinal fluid."*

Dr. Adeagbo had been warned by the Medical Microbiologist, Dr. Wilson Chan, that the test was not prime for clinical use:

> *"Broadrange PCR and sequencing for the DNA sequence coding for 16s rRNA revealed the presence of Haemophilus influenzae. However, as we discussed, while validated as an in-house assay, this test has not been verified for clinical use, especially in the specimen type of cerebrospinal fluid, and as such, should be regarded as for research use only."* (p.181 of the medical examiner's file)

The warning from the microbiologist is of crucial importance. The meaning of the result is unclear and should not have been presented in Court as a definitive proof of the presence of *Haemophilus influenzae*.

1.3.3 16S rRNA gene sequence analysis does not test for viruses

Dr. Adeago acknowledged that he did not specifically request for viral testing in the cerebrospinal fluid. However, he said, when speaking about the 16S rRNA gene sequence analysis: *"It did not tell me or provide me any other bacterial infection or any other viral infection."* (p.35)

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[11] Daniel M. Musher. Chapter 30 Haemophilus Species. Medical Microbiology. 4th Edition. Available online: http://www.ncbi.nlm.nih.gov/books/NBK8458/

[12] Available online at: https://goo.gl/nGFebR

From this statement, it seems that Dr. Adeabgo thought this test would have been able to identify viruses as well as bacteria. However, this is not the case. This test is based on DNA that codes for a portion of ribosomes, and viruses don't have ribosomes. Therefore, this test can't be used for the identification of viruses.

1.3.4 The presence of scant Gram-negative bacilli at autopsy is most likely explained by bacterial translocation and/or agonal spread

As discussed earlier, Dr. Adeagbo excluded virus as the infectious agent for two reasons. The first one, which is erroneous, was the predominance of neutrophils (see section 1.2.1 and 1.2.2 of this report). The other was the presence of a few Gram-negative bacilli in the right lung and scant Gram-negative bacilli in the cerebrospinal fluid.

When asked (p. 66-67): *"Did a virus cause Ezekiel to die?"* He answered: *"No."* He was then asked: *"Why do you say that?"* He answered, apart for the part on the predominance of neutrophils: *"I say that because all the findings, they are not -- the autopsy findings are more in – (…) more correlate with the microbiology studies that I performed, which is the gram-negative bacilli that we found in the cerebrospinal fluid as well as in the lung."*

However, the presence of a few Gram-negative bacilli at autopsy is far from surprising. It is widely known that bacteria from the intestines, mainly Gram-negative bacilli such as Escherichia Coli, will start to spread throughout the body after death (a process called bacterial translocation). This process of bacteria spreading can possibly even start before death in situation such as life support (a process called agonal spread).

In the present case, the child suffered irreversible hypoxic and anoxic brain injury on March 13, was on life support from that date up to his diagnosis of brain death on March 16, and continued to be on life support until March 18, before the autopsy was finally performed on March 19. In this case, the presence of a few Gram-negative bacilli, particularly considering the absence of a positive culture, is of no significance for the identification of the infectious agent.

Dr. Adeagbo recognized that yeasts present in the lungs are most likely a contaminant (p. 68 "*We found scant yeast in the right lung. (…) it's usually a postmortem contamination, and in this case, it might as well be."* But for some reasons, he failed to recognize that this is also the most likely explanation for the presence of a few Gram-negative bacilli.

1.4 Association of croup and meningitis, and most likely infectious agent

When considering the association of croup and meningitis, some infectious agents are more likely than others. On top of the list is the enterovirus, which is the most common cause of meningitis and a common cause of croup. Possible bacteria include *Group A. streptococci*, *Haemophilus influenzae*, *Staphylococcus aureus*, and some less common other possibilities.

It is not possible in this particular case to confirm which infectious agent caused the croup and meningitis. Considering the most common agents, and considering a positive viral test for enterovirus or rhinovirus, the most likely agent is the enterovirus. However, it is not possible to exclude the possibility of bacteria or other viruses.

2. Expected outcomes of croup and meningitis

In the absence of the medical misadventure during the paramedic intervention, the expected outcome for this child was good.

Croup alone is usually a benign condition. Only 1% to 8% of patients require hospitalization, and less than 3% require intubation (Zoorob et al 2011).[1]

Viral meningitis are usually mild and resolve without treatment.[9] However, it can sometimes happen that enteroviral meningitis have a more aggressive course, with seizures and coma (Tan et al 2016).[7] Nevertheless, studies of enterovirus outbreaks have shown that the expected outcome is of virtually 100% survival with no sequelae (Tan et al 2016[7] – on 206 children with enterovirus meningitis; Wolfaardt et al 2014[9]– on 33 children with enterovirus meningitis; Osterback et al 2015[8]– on two outbreaks in Finland, with 147 patients including 27 children and adolescent studied more closely for clinical characteristics).

In bacterial meningitis, which is known to be more aggressive than viral meningitis, the death rate varies from 5% to 10% (de Jonge et al 2010; Madagame et al 1995).[13,14] If the management of a child with bacterial meningitis required an intubation, the fatality rate is of approximately 31% (Madagame et al 1995).[14]

Therefore, without the medical misadventure during the paramedic intervention, the outcome in this case would have most likely been good. On balance of probability, this child would have most likely survived.

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[13] de Jonge RC, van Furth AM, Wassenaar M, Gemke RJ, Terwee CB (2010) . Predicting sequelae and death after bacterial meningitis in childhood: a systematic review of prognostic studies. BMC Infect Dis. 10:232

[14] Madagame ET, Havens PL, Bresnahan JM, Babel KL, Splaingard ML (1995). Survival and functional outcome of children requiring mechanical ventilation during therapy for acute bacterial meningitis. Crit Care Med. 23(7):1279-83.

3. Impact of the delay of antibiotics

It is important to note that even if this meningitis had been bacterial (which is by no way certain here, since an enterovirus seems more likely as the infectious agent), a delay in the prescription of antibiotics would more likely have had no consequences on the outcome. Indeed, it has been established that a delay in prescribing antibiotics in bacterial meningitis in children does not significantly affect the outcome.

In 1992, Radetsky completed a meta-analysis of 22 studies from 1962 to 1990.[15] His conclusion was:

> *"The author concludes that (…) a delay of less than 3 to 5 days does not appear to alter the risk of sequelae or death." He then commented on the importance of this conclusion: "Comment: The assumption that any delay in the administration of antimicrobial therapy might be associated with an increased number of sequelae and a worse outcome of bacterial meningitis has been the basis for malpractice claims against physicians and hospitals, who have been accused of failure to diagnose and treat bacterial meningitis promptly."*

More recently, de Jonge et al (2010)[13] reviewed 31 studies from 1960 to 2009. They could not demonstrate that a delay up to 48 hours before starting the antibiotics was an independent factor associated with an increase risk of death or sequelae (*"these factors have not been found in more than one study of moderate/high quality for a specific outcome category"*).

In this particular case we don't know the infectious agent. Even if the agent was a bacteria, a delay in starting the antibiotics would not have significantly increased the risk of death.

4. Cause of the irreversible hypoxic and anoxic brain injury

The child arrived at the hospital with hypoxic and anoxic brain injury. Two possible causes for this condition must be considered:

a) It is possible that the respiratory arrest from the croup/meningitis (one condition or the other, or a combination of both conditions) had already caused an irreversible hypoxic and anoxic brain injury prior to the arrival of the paramedics. This hypothesis is less likely considering that CPR was immediately started at the onset of the respiratory arrest and considering that the length of time since the arrest was still relatively short.
b) It is also possible that the hypoxic and anoxic brain injury has been caused by the medical misadventure with the paramedics being unable to re-establish proper ventilation for more than 8 minutes after their arrival.

[15] Radetsky M (1992). Duration of symptoms and outcome in bacterial meningitis: an analysis of causation and the implications of a delay in diagnosis. Pediatr Infect Dis J. 11(9):694-8.

This is the most likely cause of the hypoxic and anoxic brain injury in this case.

Of note, we don't know the duration necessary to cause hypoxic and anoxic brain injury (Garrido & Bayarri 2012).[16] It is usually thought that neurons can tolerate about 20 minutes of ischemic anoxia (Garrido & Bayarri 2012).[16]

Considering the usual favorable outcome of croup and meningitis even when requiring intubation, it is most likely, on balance of probability, that there would not have been an irreversible hypoxic and anoxic brain injury in the absence of the medical misadventure during the paramedic intervention. On balance of probability, it is more likely that the child would have survived if not for this medical misadventure.

4.1 The absence of neuron eosinophilic changes does not exclude an irreversible brain damage secondary to the paramedic's failure to establish proper airway ventilation

Dr. Adeagbo acknowledged that the medical misadventure could have caused the irreversible hypoxic and anoxic brain injury. He was asked (p. 133): "*It's just hypothetically speaking, though, is if the ambulance couldn't get air into Ezekiel -- you had used the figure seven minutes when I had suggested eight minutes so let's go with your seven minutes -- that in itself could cause brain damage; right?"* Dr. Adeagbo answered (p. 134): *"Yes, it could."*

But he later said (p. 140): *"You see, from the pathology point of view, there are actually -- there are actually findings in the brain that would indicate hypoxic encephalopathy that will indicate that a brain is as -- is sufficient blood supply or oxygen. (…) When I did autopsy, I look at the brain. There is nothing in the brain, in the spinal canal, on the brain, the substance of the brain, that shows that the cells in the brain, the neurons, are actually behaving like neurons that lack oxygen. They are not eosinophilic. They don't have that change that will suggest to me there is hypoxic encephalopathy in the neuron. (…) There is nowhere you see eosinophilic neurons. There is nowhere you see changes sufficient enough to -- I mean, changes that will suggest hypoxic encephalopathy. If there's hypoxic encephalopathy in this case, I would mentioned it, but it's not there.*
So, yeah, I agree with you of that possibility, and to mention who actually made that statement when a brain is not functioning, but the fact is the brain-dead in this case can be attributed to the meningitis, not to the hypoxic encephalopathy."

He later cited parts from his testimony at the preliminary inquiry, where he explained what are eosinophilic neurons (p. 163) : *"eosinophilic neurons (…)*

[16] Garrido M, Bayarri JG (2012). Hypoxic Encephalopathy, Miscellanea on Encephalopathies - A Second Look, Dr. Radu Tanasescu (Ed.), ISBN: 978-953-51-0558-9, InTech, Available from: http://www.intechopen.com/books/miscellanea-on-encephalopathies-a-second-look/hypoxic-encephalopathy

what does that looks like? A It's a -- there's a particular change in the brain cells that makes it to change colours for the cytoplasm and the brain cells and the nucleus change colours. They become more pinkish."

The reality is that neuronal eosinophilic changes are not to be expected in this case. This "classic" change with vivid pink neurons is the first recognizable stage following hypoxic or anoxic damages to the brain. However, after approximately 24 hours of survival, the pink appearance of the neurons will have usually disappeared. For example, we can read in Forensic Pathology: A Practical Review of the Fundamentals, by Itabashi (2007)[17]:

> *""Classic" ischemic cell change is the first change which can be recognized with confidence in human autopsy material. The cell body is variably shrunken, stains more or less intensely with aniline dies, and the cytoplasm tint varies from vivid pink to reddish with H&E stains." "This stage is said to persist in humans for at least 6 hours." "The stage of "homogenizing cell change" is characterized by disappearance of incrustations, increased homogenation and loss of staining intensity of the cytoplasm (…) This change is typically seen after 24 hours' survival." "The final stage is a "ghost cell" appearance, with cytoplasm reduced to absent around a shrunken dark-staining nucleus, and eventual cell loss." (p. 298 to 300)*

After 5 days under life support, to not find eosinophilic changes has no particular meaning. This does not exclude irreversible brain damage secondary to the incapacity to allow for proper ventilation during the paramedic intervention.

Contrary to the statement of Dr. Adeagbo, the microscopic examination of the brain reveals changes consistent with hypoxic and anoxic brain injury. As expected after 5 days under life support, there are few remaining eosinophilic neurons (though some residual ones can be observed in the cerebellum and the hippocampus). However, neuronal loss, a ghost cell appearance, and gliosis are observed in the hippocampus. In the cerebellum, there is a loss of Purkinje cells with a few remaining sinking vividly eosinophilic ones. These changes are consistent with hypoxic and anoxic brain injury dating from a few days.

5. Pleural empyema and aspiration pneumonia

A pleural empyema is found at autopsy. A pleural empyema is a collection of suppurative fluid in the pleural space. It is usually a complication of pneumonia, although other less common causes exist (e.g. penetrating chest trauma, esophageal rupture, complication from lung surgery, etc).

Dr. Adeagbo testified, as he was trying to explain the concept of organizing empyema, that pleural empyema evolves in 2 phases (p. 32-33): *"So what really*

[17] Available online at: https://goo.gl/Hbs66v

happen is that they now becoming organized. So you have the first phase, the second phase." However, it is widely known that pleural empyema evolves in 3 phases:

> *"The American Thoracic Society breaks an empyema down in to 3 stages: early exudative, intermediate fibrinopurulent, and late organizing."*[18]

In the present case, the microscopic examination reveals that the empyema is not in the organizing stage, as described by Dr. Adeagbo, but in the intermediate fibrinopurulent stage.

Dr. Adeagbo was asked: *"So why do you say that this empyema in the right lower-lung lobe is a cause of death or a reason for death of Ezekiel's Stephan?"* (p. 26). Dr. Adeagbo answered: *"the reason why I said that is because in lung with encased empyema cannot function the way it should, which means that Ezekiel would be short of breath, would be weak because of inadequate oxygenation"*.

However, pleural empyema in itself, particularly when found on only one lobe of the lung, does not cause inadequate oxygenation. The symptoms of empyema are:

> *"Patients typically present with subtle symptoms, most commonly failure to thrive, with anorexia, weight loss, and poor energy." (Worrell and DeMeester 2014).*[18]

If a patient with pleural empyema presents desaturation (inadequate oxygenation), it is usually not because of the empyema itself but because of the underlying pneumonia:

> *"Symptoms, including fever, cough, tachypnea, desaturation, and leukocytosis are usually associated with the underlying cause, such as pneumonia, and are not always present."* (Worrell and DeMeester 2014).[18]

Pleural empyema can be a cause of death in itself. However, deaths by empyema alone occur after months or years of evolution, not in terms of two weeks or less (White et al 2015).[19] Furthermore, considering the elements in this case (normal blood urea, age, purulent empyema, and low albumin), the risk of death by 3 months was of only 1.5% (White et al 2015)[19], with an even significantly lesser risk of death at the time Ezekiel actually stopped breathing. If

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[18] Worrell SG, Demeester SR (2014). Thoracic emergencies. Surg Clin North Am. 94(1):183-91.

[19] White HD, Henry C, Stock EM, Arroliga AC, Ghamande S (2015) . Predicting Long-Term Outcomes in Pleural Infections. RAPID Score for Risk Stratification. Ann Am Thorac Soc. 12(9):1310-6.

we look at the prognostic for studies on children only, then the mortality rate is closer to 0% (Krenke et al 2016; Long et al 2015).[20,21]

If Dr. Adeagbo was so concerned about the empyema as being one of the two causes of death (along with meningitis), then it raises the question of why he did not sample the empyema for microbiology. There was a higher probability of being able to identify the infectious agent in the empyema than in the lung samples or the blood:

> *"The antibiotics are not initiated for treatment of the empyema but for treatment of the underlying pneumonia. In the absence of an underlying pneumonia, no antibiotics should be used, because they cannot enter the pleural space and therefore offer no benefit to the patient."* (Worrell and DeMeester 2014).[18]

Of note, several authors are less vindictive about the inutility of antibiotics in pure empyema – nevertheless, the absence of culture of the empyema is a lost opportunity in this case. Furthermore, the relative difficulty for the antibiotics to enter the pleural cavity explains why the empyema persisted despite the antibiotics.

5.1 The empyema is most likely secondary to aspiration during the paramedic intervention

Pulmonary aspiration (i.e. the inhalation of oro-pharyngeal or gastric content into the respiratory tract) is a well-known complication of emergency intubation.

An initial chest x-ray was performed on March 13, 2014 (no specific time can be found on the report), and revealed only atelectasis bilaterally, with a large amount of air in the stomach. On this initial chest x-ray, there was no evidence of pneumonia or of pleural effusion. The following chest x-ray, performed approximately 2h30 after the paramedic intervention (March 14, 0035 hours, see p. 122 of the Medical Examiner's file), described an early phenomenon: *"The right hemithorax is diffusely more opaque than the left suggesting a pleural effusion layering posteriorly. Mildly predominant perihilar markings with additional haziness in both the suprahilar and right infrahilar regions which could represent atelectatic changes or possibly pneumonia."* Another chest x-ray, on March 14 at 5h39, stated: *"Faint added opacities of the right upper lobe, in keeping with subsegmental atelectasis noted. A small right pleural effusion is also noted."* Several hours later, the chest x-ray revealed (March 14, 1837 hours, see p. 790

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[20] Krenke K, Urbankowska E, Urbankowski T, Lange J, Kulus M. Clinical characteristics of 323 children with parapneumonic pleural effusion and pleural empyema due to community acquired pneumonia. J Infect Chemother. 2016 Feb 23 [Epub ahead of print]

[21] Long AM, Smith-Williams J, Mayell S, Couriel J, Jones MO, Losty PD. 'Less may be best'-Pediatric parapneumonic effusion and empyema management: Lessons from a UK center. J Pediatr Surg. 2015 Aug 12.[Epub ahead of print]

of the medical file): *"Patchy added densities of the right upper and lower lobes, as well as left upper lobe, noted. There is also a small right pleural effusion."*

Of note, there was no full-blown empyema nor underlying well-developed pneumonia on these chest x-rays of March 14. Therefore, it is safe to exclude the theory of Dr. Adeagbo that the child presented with organizing empyema at the time of the medical crisis on March 13.

Considering all of these elements, the pleural empyema is most likely a secondary infection caused by aspiration during the medical intervention. Aspiration pneumonia is more often localized to the right lower lobe of the lung, like in this case.

Dr. Adeagbo stated: *"And this possibility would be that the -- the right lung, the inertia of the right lung is -- is that it is the -- the way it is postured in the body is that if somebody tends to aspirate, they aspirate into the right lung because of the anatomy of the right lung. But in this case, we don't see any evidence of aspiration."*

Therefore, Dr. Adeagbo recognized the likeliness of aspiration in this case, but then ruled it out based on the absence of evidence of aspiration at autopsy. Dr. Adeagbo also stated that at autopsy, there is an empyema of the lower lobe of the right lung without residual pneumonia. However, he had written earlier, in a continuation note done immediately after the autopsy on March 19, 2012, that he had observed a "right lung consolidation" (p. 37 of the medical examiner's file), which means a pneumonia. He later excluded this diagnosis based on the microscopic examination of the lung.

However, the autopsy pictures confirm the presence of a right lung consolidation (pneumonia). The microscopic examination is consistent with a resolving aspiration pneumonia (abundance of giant cells with phagocytic vacuoles).

6. Other issues with Dr. Adeabgo's statements

6.1 Petechiae and lack of oxygen are not causally related

Dr. Adeagbo observed at autopsy the presence of petechiae on the pleura and the pericardium.

Dr. Adeagbo stated in his testimony that petechiae were caused by lack of oxygen (p. 59): *"petechiae (…) It could be -- different ways, but usually indicate lack of oxygen."* He further explained the presence of petechiae by saying (p. 60): *"I would think this would be due to the depression of the respiration from the brain, as well as the lung not be (sic) able to expand properly."*

These statements are not in line with the current scientific understanding. Petechiae are pinpoint hemorrhages resulting from the rupture of small vessels. They are not caused by lack of oxygen (asphyxia), but by other mechanisms, usually by mechanical increased pressure inside the blood vessels:

> *"the speculation that hypoxia must play a role has generated the erroneous conclusion that petechiae and asphyxia are causally related."* (Ely and Hirsch 2000)[22]

Dr. Adeagbo also stated that CPR can cause petechiae (p. 61). Though this point is still controversial, there is more and more consensus that CPR does not cause petechiae (Clement et al 2011).[23]

6.2 There is no evidence of brain herniation in this case

A head computed tomography (CT) scan performed on March 14 does not reveal brain herniation in this case. The report stated: "*This is in keeping with a diffuse cerebral edema as result of a diffuse hypoxic insult. (…) There is no tonsillar herniation seen. (…) No cerebellar tonsils herniation."*

These findings are corroborated at autopsy: Dr. Adeagbo does not describe any type of brain herniation. This can be confirmed on the autopsy pictures. Furthermore, he did not observe a bulging fontanelle, despite that the anterior fontanelle is still open.

Nevertheless, Dr. Adeagbo invoked in his testimony the presence of brain herniation to explain the cardiorespiratory arrest: *"So if you now have a pus collecting in the brain, what happen (sic) is that that is something that it's not designed for. That is something occupying a space that is not there, that is not available. So what happened is that that pus -- we (sic) affect the brain. It pushes the brain down"* (p. 27). He later continued (p. 38-39): *"it affects the function of the brain. It affects -- because the brain's now becoming squished -- now becoming squeezed in the process. (…)The part of the brain affecting the -- controlling the respiration become weak so the person have shallow breathing, tired breathing. The -- the part of the brain that control the heart become weak so the heart start not working fine, losing beats, getting weaker."* He added (p.150): *"the brain stem is in the low (sic) almost position of the brain so that it could be pushed down, which you see evidently in any brain edema; it could be pushed down."*

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[22] Ely SF, Hirsch CS. Asphyxial deaths and petechiae: a review. J Forensic Sci. 2000 Nov;45(6):1274-7.

[23] Clément R, Guay JP, Redpath M, Sauvageau A (2011). Petechiae in hanging: a retrospective study of contributing variables. Am J Forensic Med Pathol. 32(4):378-82.

These explanations from Dr. Adeagbo during his testimony are irreconcilable with his autopsy findings. In the present case, there is no tonsillar herniation compressing the respiratory and cardiac center in the brainstem.

If the meningitis caused the respiratory arrest in this case, other mechanisms must be invoked here: infectious shock with impaired blood flow to the brain, or toxic metabolic encephalopathy (by direct neuronal damage from the infectious agent, or by host reactions irritating the brain). However, considering the first 911 call, it seems more likely that the cause of the respiratory arrest on March 13 was related to the respiratory obstruction from the croup.

6.3 Autopsy report must present the pertinent negatives

Dr. Adeagbo stated in his testimony (p. 155) that he did not write in his autopsy report the absence of hypoxic injury (errorneous statement – see section 4) because *"It's about me only trying to write positive things. That's my style at that time."*

This is a surprising statement for two reasons. First, because it is well known that autopsy report must not only include positive findings, but also the pertinent negatives findings:

> *"The body should be examined in a systematic manner and the positive and pertinent negative findings recorded."* (Guidelines for medicolegal autopsies in Canada)[24]
>
> *"It is important to clearly state all of the injuries and other significant findings discovered at autopsy. However, it is equally important, and sometimes even more important to state pertinent negatives when they are deemed significant."* (Forensic Pathology: Principles and Practice)[25]

Second, it is surprising because Dr. Adeagbo did not only mention positive findings in his autopsy report, but listed several other pertinent negative findings: for example, *"free of atherosclerosis"*, *"no occlusive thrombi"*, *"atrial and ventricular chambers are not dilated"*, etc.

Of note, there is no mention at all on the certificate of medical examiner, the autopsy report form or the autopsy report about the issues during the paramedic interventions that prolonged the period of respiratory arrest by approximately 8 minutes. This omission is hard to explain, since it was obviously an important fact to report when summarizing the clinical history of Ezekiel Stephan.

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[24] Available online: http://stage.cap-acp.org/cmsUploads/CAP/File/guidelines_mediocolegal_autopsies_in_Canada2008%281%29.pdf

[25] Available online: https://goo.gl/4bfsgG

Summary

In summary:

a) This child was suffering from both croup and meningitis.
b) The infectious agent in this case can't be determined with certainty. An enterovirus is the most likely infectious agent, but a bacteria or other virus can't be ruled out.
c) There is no scientific evidence to support *Haemophilus influenzae* as the infectious agent in this case.
d) The irreversible hypoxic and anoxic brain injury is most likely secondary to the medical misadventure during the paramedic intervention.
e) The lung empyema is most likely secondary to aspiration during the paramedic intervention.
f) In the absence of the medical misadventure during the paramedic intervention, it is most likely that the child would have survived.
g) There is no scientific evidence to support that a delay in the initiation of antibiotics would have increased the risk of death in this child, even if bacterial meningitis had been the infectious agent (but there is no scientific evidence in this case that the infectious agent is a bacteria)

Sincerely,

//Electronically signed// April 16, 2016, 1006hours//

Dr. Anny Sauvageau
Forensic pathologist