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Optimal approaches to data collection and analysis of potential immune mediated disorders in clinical trials of new vaccines

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ABSTRACT

Background: The potential for development of autoimmune diseases after vaccination with new vaccines containing novel adjuvants is a theoretical concern. Randomised, placebo-controlled trials are the best method for assessing a potential causal relationship between an adverse event and vaccination, but usually have a sample size too small to detect adverse events occurring in <1% of subjects. Incomplete case documentation may hamper definitive diagnoses, preventing accurate causality assessment. To date there are no guidelines for collection, documentation and monitoring of potential immune mediated disorders (pIMD) reported in the course of clinical trials with adjuvanted vaccines.
Objective: This paper proposes a methodology for collection of pIMDs in clinical vaccine trials, with the objective of obtaining complete and reliable data using standardised methodology for its collection and analysis.
Recommendations: The role of the study investigator in prospective, standardised safety data collection is key and can be facilitated by providing a pIMD list in study documents and disease-specific standard questionnaires to assist timely and thorough documentation. External expert review of histopathology samples or other specialised diagnostic data would increase diagnostic accuracy. Centralised case ascertainment using standard case definitions would identify true cases of interest. We propose collection of safety data for at least 6 months and up to one year after the last vaccine dose. Bio-banking as a platform for collecting samples from enrolled patients for future use (e.g., to measure biomarkers of diagnostic, prognostic or predictive utility) could eventually provide valuable information in cases where a pIMD is diagnosed during the study period.
Conclusion: Standardised collection of safety data to allow appropriate analyses are optimal approaches for detecting rare events in clinical trials. Appropriate data analysis will then more reliably define potential causal relationships with vaccination.

1. Introduction

Adjuvants are used in vaccines to direct and enhance immune responses to target antigens. For around 80 years the only adjuvant used in human vaccines was aluminium salts. However, a growing number of new generation vaccines employing novel adjuvants have become available in the last 20 years [1]. Regulatory authorities, health care professionals and the general public regularly question the safety of new generation vaccines, particularly their possible effects on the regulation of the immune system and the potential (yet theoretical) concern for the development of autoimmune syndromes after vaccination.

Autoimmunity results from complex interactions between genetic traits and environmental factors, and can be triggered by a number of stimuli. Infections have long been proposed as environmental triggers for the induction of autoimmunity. For example, *Campylobacter jejuni* infection is linked with the occurrence of Guillain-Barré syndrome, associated with a cross-reacting antiganglioside antibody response [2]. However, most infections and virtually all vaccinations in humans, except for the administration

Abbreviations: AESI, adverse events of special interest; pIMD, potential immune mediated disease.

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of an old rabies vaccine that was cultivated on rabbit brain tissue [2], lack well-established links to autoimmune diseases. Case reports of autoimmune diseases temporarily associated with the administration of vaccines (both adjuvanted and non-adjuvanted) have been described in the scientific literature [3]. Most of these reports refer to vaccines targeting viral illnesses [4,5]. Proposed mechanisms by which vaccines might induce autoimmune diseases are frequently extrapolated from the known capacity of the infectious agents that the vaccine targets [3,6–10]. For vaccines targeting viral illnesses, this hypothesis is supported by animal models of virus-induced autoimmunity [11]. Among reports of autoimmune diseases for which vaccination has been suspected as the trigger in predisposed individuals, only a few have been well described and documented [2,3,12]. For example, an association between the onset of Guillain-Barré syndrome and influenza vaccination was claimed during the 1976–1977 swine flu immunisation campaign in the United States (but not in subsequent campaigns) [13–16]; similarly, idiopathic thrombocytopenic purpura was associated with the administration of combined measles-mumps-rubella vaccination in children [17]. By contrast, large epidemiological studies have failed to show associations between hepatitis B vaccination and demyelinating diseases including multiple sclerosis [18–20].

Systematic pre- and post-licensure monitoring of vaccine safety is critical in providing ongoing evaluation and signal detection of new or unexpected adverse events occurring after vaccination. Prospective collection and analysis of adverse events of special interest (AESIs) is essential in well-conducted clinical trials. Incomplete detail to support a given diagnosis and/or to consider other possible causes is one of the frequent limitations in their evaluation.

To date there are no specific guidelines for collection, documentation and monitoring of potential immune mediated disorders (pIMD) as AESIs reported in the course of clinical trials with adjuvanted vaccines. This paper proposes a standardised methodology based on experience gathered in the past few years, for the prospective collection of pIMDs in vaccine clinical trials sponsored by GlaxoSmithKline Vaccines, with the objective of obtaining complete and reliable data and for its analysis.

2. Collection of potential immune mediated disorders in clinical trials

The pIMDs are a subset of immune mediated inflammatory disorders which may or may not have an autoimmune aetiology. In immune mediated inflammatory disorders, tissue damage results from self-directed inflammation due to activation of innate immune cells, including macrophages and neutrophils. By contrast, autoimmune diseases can be classified as inflammation against self that is mediated by the adaptive immune system, with development of immune reactivity towards native antigens. Hyper-reactivity of both T and B cells (as well as aberrant dendritic cells) is typically observed in conjunction with autoantibodies and antigen-specific T cells targeting self, resulting in tissue destruction. Autoimmune diseases can cause multi-organ involvement, but the primary end-organ target typically drives the clinical presentation and disease definition [2,12,21].

The mechanisms underlying immune mediated disorders are diverse and complex, and are not fully understood to this day. Indeed for some immune mediated diseases, an autoimmune mechanism has not been clearly demonstrated. Thus, a conservative approach would be to collect data pertaining to all possible immune mediated diseases for which an autoimmune-dependent mechanism has been postulated, even if not yet firmly established (for example, psoriasis, erythema nodosum, and many others).

Vaccine clinical trials are conducted in a variety of settings and by clinical teams with varying interests and specialties. Adverse events are most frequently reported through the investigator. Therefore, investigators need to be encouraged in the prospective, standardised collection of high quality safety data, and be given tools to facilitate this process. To this end, a list of pIMDs included in study documents would focus investigators' attention on those events (regardless of seriousness), and encourage prospective reporting of any new pIMD or exacerbation of a pre-existing pIMD (serious or non-serious) in a study subject. This list of pIMDs could be limited to specific disorders that likely represent an autoimmune or immune mediated inflammatory process. Disease-specific standard questionnaires provided at study start would facilitate timely and thorough documentation of these AESIs. An example of the type of data to be collected on a disease specific questionnaire for Guillain-Barré syndrome is given in Table 1. Finally, centralised, external expert review of histopathology samples or other specialised diagnostic data is sometimes useful for diagnosis ascertainment in selected cases with a suspected causal association with the study vaccine.

Table 2 shows a proposed, non-exhaustive list of pIMDs that could be included in a study protocol as AESI. Any list proposed for inclusion in study protocols needs to balance sensitivity and specificity. A list of corresponding terms for each disease linked to a terminology dictionary would facilitate database encoding and targeted periodic searches for safety monitoring. To increase detection of these events, investigators should be asked to exercise his/her medical and scientific judgement in identifying any other reported diseases/disorders (other than those proposed by the sponsor in study protocols) having a possible autoimmune origin as a pIMD, based on the available clinical information. It is important to reiterate that the list of pIMDs given in Table 2 is not exhaustive given the ongoing evolution of this field. For example, diabetes mellitus type II is not included in Table 2, but recent data suggest that type II diabetes may be an autoimmune mediated disease [22,23]. Furthermore, many immune-mediated diseases have symptoms that are non-specific (such as 'arthralgia') which also have a high prevalence in the general population. Thus, symptoms, signs or conditions without evidence of pathophysiology involving pathogenic immune processes and for which further clinical investigation and immunological tests must be done to explore the possibility of a putative autoimmune origin should be recorded and reported as adverse events, but not as pIMDs, until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.

3. Exacerbation of existing pIMDs

It has been a matter of debate whether vaccination has the potential to exacerbate pre-existing autoimmune diseases. Concerns that vaccination in subjects with pIMD might trigger a flare, affecting the course of disease or disease activity, have been postulated often in case reports or in studies of small numbers of subjects [24–27]. Investigations of selected vaccines and diseases have generally failed to identify causal links [2,14,28–37], although not all vaccine-disease combinations have been evaluated. In this respect, the collection of adverse events related to an exacerbation of a pre-existing pIMD after vaccination should also be considered. In these cases clinical status evaluation and laboratory testing before vaccination may be required to distinguish between new onset and pre-existing disease.

Table 1
Example of data to be collected in the event of a pIMD, in this case, Guillain-Barré syndrome (GBS).

Reporter details	Report date
	• Reporter name/contact information/qualifications/location
Vaccinee demographic details	• Case or study participant identifiers/date of birth (gestational age and weight at birth, APGAR score if applicable).
Clinical and immunisation history of the subject	• Medical history of any pre-immunisation condition including pre-vaccination neurological status • Drug/toxin and medication history Immunisation history • Details (clinical or laboratory) of antecedent infectious illness within 6 weeks prior to onset of neurologic signs • Immunisation details including date/description/lot/site/administration route
Description of the adverse event	• Criteria fulfilling the case definition and other signs/symptoms indicative of GBS, including autonomic manifestations • Description of clinical manifestations and course including clinical findings, laboratory features, electrophysiologic features suggestive of GBS: – Severity of weakness at clinical nadir – Disease duration between clinical onset and nadir – Additional neurologic signs – Concurrent signs, symptoms, and diseases – Results of all electroneuromyographic studies – Results of neurophysiologic studies, including electroencephalography and neuroimaging studies – Results of cerebrospinal fluid examination – Results of antiglycolipids antibodies – Additional laboratory testing results identifying an aetiology other than GBS • Date/time of onset. First observation of diagnosis • Results of neurologic consultation including assessment of: – Manual Muscle Testing (Medical Research Council Scale) – Deep tendon reflexes – Sensory examination – Cranial nerve – Presence or absence of ataxia – Modified Rankin Functional Score – GBS disability score • Regular measurement of clinical parameters at: – Initial presentation – Clinical nadir – Points of significant clinical change – Recovery • Record outcome including neurologic function/clinical status/ongoing treatment

Adapted from guidelines discussed in [38].

4. Onset and duration of data collection

It is not uncommon that the first signs and symptoms of a pIMD can occur months to years before a diagnosis is made. For many diseases the time to disease onset after a triggering event is unknown. Thus, both the time to onset and the time to diagnosis are highly variable, depending on the disease concerned and the individual affected. Consequently, the pIMD data collection period in vaccine clinical trials has to be determined using a theoretical risk period after the last vaccination, where the likelihood of observing an increased risk for developing potential immune mediated disorders would be highest if there was a causal link between the disease and vaccination. This theoretical risk interval should ideally be determined based on the onset of the disease (either acute or insidious), possible or known pathologic mechanisms involved, and the type of vaccine [39]. To date, few references have formally assessed and determined biologically plausible and evidence-based risk intervals in immunisation safety research. For Guillain-Barré syndrome, the period of increased risk was shown to be concentrated within 6 weeks after the 1976–1977 swine flu vaccination [13,14]. Therefore a 6 week time window is generally used for the assessment of cases of Guillain-Barré syndrome potentially associated with vaccines [16,40]. For acute disseminated encephalomyelitis following immunisation, the risk interval also appears to decrease substantially beyond 6 weeks after vaccination [39]. Also, the possibility of a longer interval between vaccination and disease onset cannot be excluded, in particular for diseases with an insidious onset such as Multiple Sclerosis or rheumatic diseases.

Whatever the underlying mechanisms, one may assume that the development of autoimmunity (if a causal association between the event and vaccination existed) requires several weeks to develop; which is similar to the classical time frame of several weeks suggested for the onset of post-infectious autoimmune phenomena. The risk becomes very low several months following the last vaccine dose received. Assuming that in the hypothetical event of a causal association, the development of autoimmunity after vaccination requires a few weeks to develop, but is likely to be less than a few months following vaccination: thus, in the absence of definitive biological or epidemiological data, we propose that one year after the last vaccination would be a reasonable maximum theoretical risk interval for new onset of autoimmune diseases.

There are limited data to suggest the shortest risk interval between provision of an antigenic stimulus (e.g., natural infection), the mounting of a subsequent immunologic response, and onset of clinical immune-mediated disease [39,41]. An initial interval (the time window following vaccination during which an event, if it occurred, has no biological plausibility to have been triggered by vaccination), may also be considered when analysing pIMD data reported after vaccination. Assuming that the risk window begins immediately post-vaccination, we advocate data collection commencing immediately after vaccination is given. However, taking into account the biologic mechanisms by which autoimmune responses are generated and how they might lead to clinically observable illnesses, in addition to the known kinetics of primary and secondary antibody responses after exposure to vaccine antigens, an interval of less than 5–7 days post-vaccination would seem to be biologically implausible for a possible vaccine-induced pIMD [42,43].

5. Identification of predictive markers for potential immune mediated disorders in clinical trials

Biomarkers in clinical medicine are generally used to facilitate or confirm a diagnosis, to aid prognosis and to evaluate clinical

Table 2
Suggested list of potential immune mediated disorders (pIMDs) of interest for possible evaluation in clinical vaccine studies.[a]

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
Cranial nerve inflammatory disorders, including paralyses/paresis (e.g., Bell's palsy)	Systemic lupus erythematosus	Psoriasis
	Systemic sclerosis (with limited or diffuse cutaneous involvement)	Vitiligo
Optic neuritis	Dermatomyositis	Erythema nodosum
Multiple sclerosis	Polymyositis	Autoimmune bullous skin diseases (including pemphigus, pemphigoid & dermatitis herpetiformis)
Transverse myelitis	Anti-synthetase syndrome	Cutaneous lupus erythematosus
Acute disseminated encephalomyelitis including site- specific variants: encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis, cerebellitis	Rheumatoid arthritis	Alopecia areata
Myasthenia gravis (including Lambert-Eaton myasthenic syndrome)	Juvenile chronic arthritis (including Still's disease)	Lichen planus
Immune mediated peripheral neuropathies and plexopathies, (including Guillain-Barré syndrome, Miller Fisher syndrome and other variants, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy)	Polymyalgia rheumatica	Sweet's syndrome
	Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis	Morphoea
	Psoriatic arthropathy	
	Relapsing polychondritis	
	Mixed connective tissue disorder	
Narcolepsy		
Liver disorders	**Gastrointestinal disorders**	**Metabolic & endocrine disorders**
Autoimmune hepatitis	Crohn's disease	Autoimmune thyroiditis (including Hashimoto thyroiditis)
Primary biliary cirrhosis	Ulcerative colitis	Grave's or Basedow's disease
Primary sclerosing cholangitis	Ulcerative proctitis	Diabetes mellitus type I
Autoimmune cholangitis.	Celiac disease	Addison's disease
Vasculitides	**Others**	
Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis & temporal arteritis	Autoimmune haemolytic anaemia	
	Autoimmune thrombocytopenia	
Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome (allergic granulomatous angiitis), Buerger's disease (thromboangiitis obliterans), necrotising vasculitis & anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis	Antiphospholipid syndrome	
	Pernicious anaemia	
	Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, & mesangioproliferative glomerulonephritis)	
	Uveitis	
	Autoimmune myocarditis/cardiomyopathy	
	Sarcoidosis	
	Stevens-Johnson syndrome	
	Sjögren's syndrome	
	Idiopathic pulmonary fibrosis	
	Goodpasture syndrome	
	Raynaud's phenomenon	

[a] Note that this table is not intended to be exhaustive, but is indicative of the type of conditions that could be included as adverse events of special interest (AESI) in clinical trials.

progression and response to treatment. The ideal biomarker of immune mediated diseases would be one with a defined normal range that becomes abnormal when a specific autoimmune disease develops, that changes in proportion to disease severity, that becomes normal during remission, and that is detectable in serum. Autoimmune disease biomarkers under investigation may be grouped into three broad areas encompassing tissue degradation products; enzymes implicated in tissue degradation; and cytokines/other proteins that play a role in immune system activation and inflammation [44].

Biobanked samples obtained from study participants, specifically serum or plasma, at study start would enable testing for diagnostic, prognostic or predictive markers in subjects in whom a pIMD or disease flare was diagnosed during the study period. The information on the presence or absence of these markers before administration of the first vaccine dose would allow, in some cases, for a better causality assessment of pIMD cases that are reported after vaccination. However, the establishment of biobanks in the clinical trial setting may entail multiple challenges, including high cost, infrastructure and resources, difficulties obtaining consent from participants, potential liability issues, and the extensive planning required to ensure the quality and availability of samples that might also be amenable to future investigations.

5.1. Autoantibodies

Pathogenic autoantibodies directed against membrane antigens may be causative of disease. For some diseases such as Grave's disease, myasthenia gravis, pemphigus, and others, it has been clearly demonstrated that autoantibodies directly mediate the clinical phenotype and/or organ damage. Nevertheless, the value of autoimmune antibody testing in clinical trials for those pIMD where autoimmune antibodies have a known diagnostic or predictive value is not clear. The presence of autoantibodies is not in itself considered synonymous with autoimmune disease, as other clinical conditions (such as cancer, acute tissue damage) may also be associated with their presence [21]. In addition, while the detection of specific autoantibodies in serum is an important diagnostic tool for some autoimmune diseases [45,46], autoantibodies are typically poor biomarkers for reasons related to specificity, sensitivity and technical issues linked to their measurement. Normal human serum contains a spectrum of autoantibodies which are poly specific and present low affinity for a variety of autoantigens. Autoantibodies may be detected in normal individuals (for example, approximately 30% of normal persons have an anti-nuclear antibody titre $\geq$1:40 [47]), as well as in patients with autoimmune disease and patients with other inflammatory diseases. Moreover, specific autoantibodies may be detectable in the serum years before the onset of clinical disease.

Further complicating assessment of laboratory results, autoimmune diseases commonly have diagnostically overlapping features, a number of nonspecific constitutive manifestations and a variety of possible autoantibody profiles. Autoantibody positivity may be transient, that is, the autoantibodies may disappear without any evidence of clinical disease, and autoantibody levels generally do not fluctuate in relation to disease severity.

Inter-laboratory variation in detection methods including assay cut-off values, test validity and precision also hampers interpretation of results [48,49]. Different tests vary considerably in their specificity, sensitivity and clinical significance. The specificity of tests for target diseases differs between individuals with similar disorders, and the predictive value of the test is considerably affected by the prevalence of the target disease [50–54].

Based on these features it is apparent that autoantibody positivity does not necessarily lead to a diagnosis of autoimmune disease and it cannot always be easily correlated with disease onset. Indeed, the diagnostic accuracy of specific autoantibodies is extremely variable depending on different diseases and different autoantigen/autoantibody systems [45]. Pre-exposure testing for autoantibodies may, however, be useful for a few specific autoimmune diseases for which the specificity of an autoantibody is well established (e.g., islet-specific antibodies for diabetes mellitus type 1).

5.2. Non-autoantibody biomarkers

Currently, non-autoantibody biomarkers for autoimmune diseases are being used as research tools but have not demonstrated utility as clinical tools. This is because some non-autoantibody biomarkers may reach abnormal levels in individuals without clinical symptoms or signs of disease; there is a lack of assay standardisation between laboratories in terms of procedures and antigens tested; and both levels of specific biomarkers and symptoms may vary in subjects suffering from the same immune mediated disease. Nevertheless, blood samples are frequently collected in subjects prior to vaccination and analysis of both baseline samples and samples obtained at the time of the pIMD may provide valuable information in the future. For example, collected samples could feasibly be analysed for new biomarkers well after study completion, using "omic"-based approaches, which may be useful for safety assessments (e.g., genomic testing could aid identification of subsets of people at risk for certain adverse events) [55–57].

6. Signal detection and evaluation

Signal detection relies on a combination of individual and aggregate medical case review. All adverse events reported as pIMDs to investigators during the course of a clinical trial need to be medically assessed to confirm the diagnosis as definitively as possible, and to obtain relevant clinical data.

For the purposes of signal detection and analysis of data, pIMDs can be coded and retrieved from databases using pre-defined groups of terms linked to a terminology dictionary, or by constructing a customised query, which are intended to aid in identifying cases that are highly likely to represent these cases of interest.

Individual case reports need to be evaluated by a medically qualified person to confirm the diagnosis and thereby identify true cases of interest among the whole batch of potential cases identified by the search. When available, generally accepted case definitions have an important role in guiding the identification of true cases of interest, greatly facilitate the meaningful assessment of the safety data and allow for comparability of study results. Therefore, the use of standardised case definitions is strongly encouraged for integrated safety analyses [58]. Some standard case definitions are publicly available and are accepted as a reference by the general medical community. These include algorithms for the diagnosis of a disease, for example multiple sclerosis [59,60], and a growing number of standardised case definitions, such as those developed by the Brighton Collaboration (http://www.brightoncollaboration.org) for Guillain-Barré syndrome [38], encephalitis, myelitis and acute disseminated encephalomyelitis [61]. Medical evaluation generally differentiates individual cases into different levels of diagnostic certainty (i.e., levels of evidence for a reported event meeting the case definition): cases where the diagnosis is considered as confirmed, cases reported without sufficient information to conclude on diagnostic certainty, and cases for which the diagnosis is excluded. Confirmed and possible cases are generally considered for further data analysis.

Disease activity is generally assessed by the presence of clinical symptoms or standardised clinical disease activity scores. A number of disease activity scores have been established and generally accepted for several autoimmune diseases. They include scores for rheumatoid arthritis [62,63], ankylosing spondylitis [64], systemic

lupus erythematosus [65] and vasculitis [66]. Activity scores in conjunction with case definitions provide a means of assessing disease severity of new onset disease, as well as evaluating exacerbations in individuals with pre-existing immune mediated illnesses.

7. Limitations of preapproval studies to detect rare events

Safety is assessed in all phases of vaccine clinical development and should continue throughout its life cycle. Randomised controlled trials are the principal means of establishing the safety and efficacy of vaccines. However pre-approval trials are usually limited in size and duration and exclude high-risk populations, so they may have limited statistical power to detect rare but potentially serious adverse events. Effective safety data collection in clinical trials requires specific attention to facilitate its meaningful comparison and interpretation. Furthermore, a thorough medical assessment of relatively rare adverse events, such as those related to autoimmunity, is essential; as the occurrence of a single event may raise concerns, for which the quality of the data becomes critical.

8. Conclusion

This review considers means by which safety data gathering can be optimised in the clinical trial setting. Standardised collection of safety data aims to minimise under or over reporting and to maximise the quality of medical information that is collected to allow diagnostic certainty and causality assessment in individual cases. Emphasis on the importance of collection of high quality safety data to investigators can be achieved through the use of pIMD lists and targeted disease questionnaires. Data collection over a defined risk period, expert review of diagnostic tests and centralised, systematic case review using accepted clinical case definitions will allow more reliable assessments of potential causal relationships between specific pIMDs and vaccination. In the future, detection of biomarkers and/or autoantibodies may offer improved diagnostic accuracy, or prognostic and predictive utility.

Nonetheless, safety information gained in pre-licensure clinical trials represents just one means by which vaccine safety is monitored. The number of subjects in such trials may still not be large enough for the assessment of the potential for the vaccine to be associated with very rare adverse reactions. Post-approval targeted safety studies specifically planned or conducted to examine an actual or hypothetical safety concern between specific pIMDs and vaccination are sometimes required [67]. Studies conducted in patients with autoimmune diseases are of particular interest to exclude the risk of disease enhancement after vaccination [68]. Vaccines are administered to much larger populations after licensure than is possible during clinical trials. Therefore, ongoing post-licensure safety monitoring is essential in the continuing evaluation of vaccine safety [35].

Conflict of interest

FTDS is an employee of GlaxoSmithKline Vaccines and reports ownership of GSK stock options.
FDK has served as a consultant to the GlaxoSmithKline group of companies.
PHL has served as consultant to the GlaxoSmithKline group of companies.
RW has acted as a consultant to the GlaxoSmithKline group of companies.
WR has received honoraria for consultancy from the GlaxoSmithKline group of companies.
CS has received honoraria for consultancy from the GlaxoSmithKline group of companies.

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